Journal of Cannabis Therapeutics: An Editorial Introduction

It is with a great sense of anticipation and excitement that we present Volume 1, #1 of *Journal of Cannabis Therapeutics: Studies in Endogenous, Herbal & Synthetic Cannabinoids*.

This journal is devoted to the scientific examination of clinical cannabis, the biochemical mechanisms of endocannabinoids, and biosynthetic analogues that are based upon their cellular mechanisms.

We hope to educate and enlighten a broad-based readership of physicians, researchers and other health professionals as to the historical record of this controversial healing herb, its putative clinical applications in modern medicine, as well as the biochemical and pharmacological functions of cannabinoids in animals and humans. Topics pertaining to toxicology, psychology, social effects, and even pertinent political aspects of cannabis and cannabinoids will be presented in this forum.

Initially, the *JCT* will consist predominantly of review articles on the medical applications of cannabis and biochemical role of cannabinoids, whether "endo" or "*nouveau*." We will also present editorials, abstract listings, pertinent book reviews, meeting notices, and Letters to the Editor, much as other journals. Where illustrative and meritorious, we will republish archival material and translations concerning cannabis research. In the near future, we hope that contributors will submit a greater proportion of original research in these areas, as well as double-blind controlled clinical trials that are the *sine qua non* of modern human research, but have been rarely pursued in the last generation due to governmental prohibitions.

Through peer review and high standards of scientific merit and scholarship, we hope to present a publication that is educational, enlightening and relevant, if occasionally provocative.

Our format is quarterly, but will consist of two standard issues plus

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one double theme-related issue each year, so as to allow the in-depth treatment of particularly important topics.

We proudly initiate this inaugural issue with the latest contribution from the dean of American cannabis research, Leo Hollister. His legacy to our body of knowledge in this area of study is enormous, and he is well known for "speaking his mind" irrespective of the question on which side of the political fence his pronouncements may land. His review on clinical cannabis serves nicely as a point of departure on "medical marijuana," focusing as it does on a foundation of peer-reviewed modern studies. Some among our readers are certain to criticize it as "soft-pedaling" possible clinical benefits of cannabis, while others will suggest he has been too supportive. Debate is only enhanced when the presentation promotes it through a solid discussion of the issues.

The contribution of Richard (Rik) Musty and Rita Rossi presents important new information on the clinical utility of cannabis and THC in the treatment of nausea and emesis in cancer chemotherapy. Their sources derive from state-sponsored studies, previously unpublished, or even politically suppressed. This paper was recently rejected by one of the premier medical journals in the USA based on the contention that its methods did not meet modern criteria of medical proof. Those of us who reviewed it for publication in *JCT* feel otherwise, and rather, that the information is relevant and compelling. Now a wider audience will have the ability to judge the material themselves.

Vincenzo Di Marzo presents a state-of-the-art review of endocannabinoids, and their possible application to clinical medicine. It is astounding to realize that this area of research has yet to exist for even one full decade. Despite its novelty, the discovery that our nervous and immune systems are regulated in part by endogenous mechanisms biochemically related to natural cannabinoids portends to be a fertile area of bench research and clinical investigation for many years to come. Dr. Di Marzo has done an admirable job in providing a suitable foundation for building a knowledge base on this topic for those of us to which it is new.

Indalecio Lozano is a name that will be new to most of our Anglophone readership. His background is quite distinct from our other authors, as an academic in the Humanities, and professor of Semitic Languages. His offering is one that deserves promotion on the subject of cannabis therapeutics, in that he brings to us a voice that is rarely

heard: that of the medical historian, who is able to restore lost knowledge and enable us to integrate it into the larger picture of our subject. In this instance, he provides an excellent review of the use of cannabis in the Arabic medical tradition. Heretofore, this body of knowledge has been poorly presented in the Western literature, whether due to inaccessibility, barriers of language, inadequate scholarship, or outright cultural myopia. In this journal, we hope to rectify some of these oversights, and fill a few of our historical and scientific lacunae.

John McPartland presents an interesting and thought-provoking examination of anti-inflammatory effects of cannabinoid and non-cannabinoid components. Representing as it does a "hot topic" in modern medicine, this review will provide a great deal of material worthy of further reflection for anyone who ponders the clinical implications of inflammation, or wishes to divine new approaches to its treatment.

In our effort to represent archival material on cannabis therapeutics, we will periodically feature a series titled "Cognoscenti of Cannabis." The first pertains to Jacques-Joseph Moreau (de Tours), a French pioneer of psychopharmacology, and his attempts to treat a desperately ill patient, victim of "lypemania," with an extract of cannabis. This article is presented in English for the first time.

Ultimately, Jon Gettman provides us a studied political and scientific analysis of perceived inconsistencies in the legislative classification of cannabis, natural tetrahydrocannabinol (THC), and its synthetic cousin, dronabinol (Marinol®). Serious issues are examined that remain open questions in the minds of many patients and their doctors who are seeking better tools in the battle against disease.

Reviews of two recent books, *The Science of Marijuana* by Leslie L. Iversen, and *Hashish!* by Robert Connell Clarke, round out the first issue.

Some parties will certainly question the scientific basis and therapeutic relevance of this journal. Skeptics as to its ultimate viability have even included members of its Editorial and Advisory Board. As this is written, legislation is under review in the US Congress that will challenge even its very legality. Any written or electronically published material that is perceived to encourage education and dissemination of knowledge pertaining to the promulgation of illicit drugs may be subject to legal proscription.

The editor's personal bias is that broader knowledge should not be

considered subversive until or unless it is absolutely clear that it purposely harms others. In *JCT*, we have no such intent. Rather we present the hope that our efforts will enhance the health and well-being of many individuals. We will raise the questions. It will only be through further examination of the issues, and the passage of time, that proof or refutation will occur. Consensus is a slowly evolutive process, and one that is rarely complete.

The history of cannabis is a fascinating example of knowledge gained and knowledge lost. The medical writings of the Ancient Sumerians and Chinese may yet offer us insights of clinical value to modern humanity. Cannabis prohibition has been previously attempted in other cultures, and failed to stem the human instinct to challenge ordinary consciousness, and seek relief from bodily and spiritual distress. If one may forgive an irresistible etymological pun, this resilient phytomedicinal has "hit the canvas" many times in the past, only to arise once more to attain medical utility, and popular usage in a sort of historical *cannabis interruptus*.

In closing, it would seem that a remarkable herb provides us with insights and challenges as to what constitutes medicine. With modern developments on endogenous cannabinoids, cannabis has led to a better understanding of our internal biochemical make-up, and pointed the way to possible synthetic therapies that may control many current afflictions. Cannabis, the herb, remains controversial. Beyond its psychoactivity, this plant offers greater opportunities. A renewable resource for fiber, food, and nature's greatest source of healthful essential fatty acids has been made a pariah. That this occurred on the basis of a political agenda, rather than on actual danger or clinical deficiencies, is an error that history and the scientific method demand be rectified. The truth about cannabis as a therapeutic tool should be sought expeditiously, and independently of the prejudice that has hindered the advancement of our knowledge of it for some sixty years.

Ethan Russo, MD
Missoula, MT
Spring 2000

Marijuana (Cannabis) as Medicine

Leo E. Hollister

ABSTRACT. The modern published literature on the therapeutic potentials of cannabis has been reviewed. A pure preparation of the major active component, delta-9-tetrahydrocannabinol (THC), Marinol® or dronabinol, is available for treating nausea and vomiting associated with cancer chemotherapy and as an adjunct to weight loss in patients with wasting syndrome associated with AIDS. Although such approval currently applies only to orally administered THC, for practical purposes smoked marijuana should also be expected to be equally effective.

Promising leads, although often fragile, suggest possible uses for treating chronic pain syndromes, neurological disease with spasticity and other causes of weight loss. These possible indications require more study. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Cannabis, marijuana, THC, dronabinol, vomiting, spasticity, anorexia, pain, seizures, glaucoma, asthma, insomnia

INTRODUCTION

Marijuana has been used medically for millennia and in the United States for over 150 years. It was in the US Pharmacopoeia until 1942 when it was removed because of federal legislation making the drug

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Leo E. Hollister, MD, is affiliated with the Harris County Psychiatric Center, University of Texas Medical Center, 2800 South MacGregor Way, Houston, TX 77021.

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illegal. The number of potential indications ranged so widely as to rival those of patent medicines of the time (Table 1). Like the latter, all the proposed indications were based on anecdote and folklore. A few studies of the medical utility of a material thought to be similar to the active component of marijuana, synhexyl (parahexyl), were made during the 1940's and 1950's (Himmelsbach et al. 1994; Loewe, 1946; Stockings, 1947; Pond, 1948; Parker and Wrigley, 1950; Thompson and Proctor, 1953). However, it was not until the isolation and synthesis of delta-9-tetrahydrocannabinol (THC) as the active component during the mid 1960's that more formal pharmacologically based studies became possible (Gaoni and Mechoulam, 1964; Isbell et al. 1964). Nonetheless, a comparison of synhexl and THC revealed them virtually identical in clinical effects, except that synhexyl was less potent and slower in onset of action (Hollister et al. 1968). Curiously, almost all studies of medical marijuana have employed THC or its homologs rather than smoked marijuana. This oversight has created the current climate of controversy about the medical uses of marijuana.

During the past 25 years, a number of reviews have appeared touching upon the therapeutic aspects of marijuana (Nahas, 1973; Bhargava, 1978; Zinberg, 1979; AMA Council, 1980; AMA Council, 1981; Ungerleider and Andrysiak, 1985; Hollister, 1986; Hall et al., 1994; Grinspoon and Bakalar, 1995; Voth and Schwartz, 1997). As with

TABLE 1. Proposed Therapeutic Indications of Marijuana

*Antiemetic	Melancholia
*Appetite Stimulation	Neuralgia
*Antispasmodic, muscle relaxant	Antitussive
*Analgesic	Antineoplastic
*Bronchodilator	Antipyretic
*Anticonvulsant	Topical antibiotic
Sedative-hypnotic	Anti-inflammatory
Opiate, alcohol withdrawal	Obsessive-compulsive
Antihypertensive	Dysmenorrhea

*some suggestive evidence for efficacy

most issues surrounding use of marijuana, interpretation of the medical literature has been filled with controversy, ranging from those who believed it to be a panacea provided by Nature to alleviate the ills of mankind to those who believe that any acceptance of medical use will send the wrong message to young people, for whom marijuana is considered to be a menace and a stepping-stone to the use of more dangerous drugs. This reviewer will try assiduously to avoid bias as well as to place the possible medical uses of marijuana in the context of currently available alternative treatments for the same indication.

The present review will focus primarily on clinical studies evaluating proposed medical uses of marijuana published in refereed medical journals. The various indications will be discussed in the order of the amount of evidence currently available to support each. Readers may then form their own opinion regarding the overall quality of the evidence. Medical indications are divided into two categories, those with enough available evidence to merit further study and those for which evidence is so lacking or so poor as to merit little serious further consideration. Most studies will involve THC rather than smoked marijuana. The argument has been made that smoked marijuana, which contains almost 300 chemicals, few of which have been studied, might therefore have superior utility over the pure material. Although a number of cannabinoids have been found in marijuana, most with similar effects to those of THC itself, they are uniformly weaker and far less abundant than THC. Thus, customarily doses of raw marijuana have been calibrated to their THC content (Hollister 1974).

INDICATIONS WITH EVIDENCE FOR MEDICAL EFFICACY

Antiemetic Action

The antiemetic action of marijuana was not anticipated despite anecdotal reports over the years. The story is that a young patient being treated with chemotherapy for leukemia reported to his oncologists that smoking a marijuana cigarette before and during the chemotherapy ameliorated the nausea and vomiting which is routinely produced. These side effects of cancer chemotherapy are so noxious that patients may refuse life-saving treatment rather than endure them. Over time, repeated experiences of nausea and vomiting may be conditioned, so

that this adverse effect is evoked by the mere anticipation of a round of chemotherapy.

Although an antiemetic effect of THC had been suggested as early as 1972, the first report of a placebo-controlled trial came in 1975 from one of the top oncology centers in the USA. THC in the form of gelatin capsules, in which the drug was dissolved in sesame seed oil, was given in doses of 15 to 20 mg to 20 patients undergoing cancer chemotherapy. Three doses were given, 2 h before and 2 and 4 h after chemotherapy. Fourteen of the 20 patients in whom an evaluation could be made reported a definite antiemetic effect from the THC, while none was observed from placebo during 22 courses (Sallan et al. 1975).

Another comparison of THC with placebo was made in 15 patients with 11 acting as their own control. Fourteen of the 15 patients given THC obtained more relief of nausea and vomiting than from placebo during a course of high-dose methotrexate chemotherapy (Chang et al. 1979). Best results were obtained when plasma concentrations of THC were more than 12 mg/ml. Such concentrations would ordinarily be expected to produce rather definite mental effects (Hollister et al. 1981).

A larger uncontrolled study was done several years later confirming these results. Fifty-three patients refractory to other treatments were studied in an uncontrolled fashion. Ten had complete control of vomiting when THC was administered before chemotherapy and for 24 h thereafter. Twenty-eight had 50% or more reduction in vomiting, and only 15 patients showed no therapeutic effect whatsoever. However, four patients were dropped from the study because of adverse effects (Lucas et al. 1980).

In yet another comparison of THC and placebo, the former treatment was superior, but the side effects were so profound that the patients preferred avoiding treatment. However, doses were far in excess of what might be needed for efficacy, obtaining plasma concentration of 300 ng/ml of THC, several times those required (Kluin-Neleman et al. 1979).

Several studies followed with the next logical step, a comparison of THC with prochlorperazine, which was then the favored antiemetic. One of the first was by the group making the original controlled trial. Doses of 15 mg of THC were compared with 10 mg doses of prochlorperazine in a controlled crossover trial in 84 patients. THC produced

complete response in 36 of 79 courses, while prochlorperazine was effective in only 16 of 78 courses. Twenty-five patients received both drugs, of whom 20 preferred THC. Of the 36 courses of THC that resulted in complete antiemetic response, 32 were associated with mental effects characterized as a ''high'' (Sallan et al. 1979).

Another comparison between THC in 15 mg doses and prochlorperazine in 10 mg doses versus a placebo control was made in 116 patients who received oral doses 3 times a day. The THC regimen was equal to prochlorperazine, and both were superior to placebo. However, many patients who received THC found it unpleasant (Frytak et al. 1979). When THC was compared with prochlorperazine and placebo, the latter two treatments were found to differ, but THC was superior to either one (Orr et al. 1980). A controlled crossover design compared oral doses of THC 7.5 to 12 mg with oral doses of prochlorperazine in 214 patients and concluded that the two treatments were equal (Ungerleider et al. 1982).

Comparisons with other antiemetics have also been made. THC was found to be superior to either prochloperazine or metoclopramide in pediatric cancer patients. An increase in drowsiness, appetite and ''high'' were reported in patients treated with THC (Ekert et al. 1979). A crossover comparison of THC and haloperidol for treatment of 52 patients with nausea and vomiting from cancer chemotherapy compared oral doses of 10 mg/day of THC with 2 mg/day of haloperidol given alternately in two-week courses. Both drugs were equally effective. Some patients who did not respond to one drug responded to the other. Although no serious side effects were reported, THC toxicity was less well tolerated than that of haloperidol (Neidhart et al. 1981).

An uncontrolled study used 56 patients undergoing cancer chemotherapy that had not responded to standard treatment for prevention of nausea and vomiting. After being allowed four marijuana cigarettes daily during the course of chemotherapy, 78% benefited. Young age and previous experience with cannabis were predictors of good response. Sedation and dry mouth were the only side effects (Vinciguerra et al. 1988).

A review of dronabinol (oral THC) cancer chemotherapy patients treated for nausea and vomiting indicated that combination with prochloperazine was more effective than either drug alone. Among 750 courses of therapy with THC, about one-third each of patients had considerable response, partial response or no response. In open studies

of appetite stimulation among patients with either cancer or symptomatic HIV infections, doses of 2.5 mg twice daily were effective in stabilizing weight and improving appetite (Plasse et al. 1991).

Although smoked marijuana is often preferred, whether it is superior to orally administered THC has not been tested in controlled comparisons. It may very well be those pharmacokinetic differences between orally administered THC and smoked marijuana might explain the preference for the latter route. Orally administered THC is slow in onset of action though longer in duration. Smoked marijuana produces a THC concentration that mimics the pattern of intravenously administered THC (Agurell et al. 1986). This immediate effect might be perceived by patients as more desirable. For those patients who have this perception, smoked marijuana may be the drug of choice. Smoking marijuana cigarettes, even at street prices, would certainly be less expensive than using conventional antiemetic drugs.

An oral preparation of THC (Marinol®, dronabinol) has attained approval for two indications. Nausea and vomiting associated with cancer chemotherapy are still something of a problem with usual anti-nauseants and THC has been shown to be an effective treatment compared with prochlorperazine (Lane et al. 1991). Severe weight loss associated with the wasting syndrome experienced by patients with AIDS is another indication less well established. No comparisons have been made with other possible treatments, either 5-HT_3 receptor antagonists or anabolic steroids, such as testosterone.

A survey that questioned members of the American Society of Clinical Oncology obtained responses from 1,035 members. About 44% of the responders told of using illegal marijuana for the treatment of at least one patient and almost one-half would prescribe marijuana were it to be made legal. Respondents also were of the opinion that marijuana itself was more effective than THC or semisynthetic cannabinoids (Doblin and Kleiman 1991).

A later survey of oncologists in 1993 by means of questionnaire obtained replies from 141 physicians. The major question was how they would rank available antiemetics for such use (Schwartz 1994). The four favored drugs were metoclopramide, lorazepam, dexamethasone or other corticosteroids, and prochlorperazine or promethazine. Marijuana or oral THC (dronabinol) was rated sixth in preference. Of those oncologists who had prescribed marijuana or THC for their patients, the drug was considered efficacious in about 50% of patients.

However, one in four patients complained of bothersome side effects. By the time of the survey, prescriptions for marijuana had declined. Few oncologists reckoned that they would prescribe the drug more frequently were it made legal and freely available. This survey was completed before the availability of 5-HT_3 antagonists, such as ondansetron, which would currently be the first choice in treatment. Neither did it consider the efficacy of combinations of antiemetics, which have often surpassed the efficacy of single drugs.

In summary, one can conclude that marijuana, both taken orally as THC or smoked, is effective in controlling nausea and vomiting associated with cancer chemotherapy being comparable in efficacy to some currently used antiemetics. As this indication is already approved for the oral form, and as no evidence indicates that the effects from smoking are qualitatively different, one might accept the use of smoked marijuana for the same indication. The choice of dosage form could then be made based on whether a rapid-acting short-lived effect was preferable to a slow-onset, longer duration of action. One might even imagine scenarios in which both dosage forms might be used together. Although evidence for efficacy of the smoked form is less than optimal, in part due to less opportunity for such studies, it is now at least as convincing as was the evidence for orally administered THC. The admission of smoked marijuana as an acceptable treatment for this specific indication would be justified on the basis of present knowledge and would save both much effort and expense by avoiding the need for their elegant proof of efficacy demanded for drugs with the less well-known efficacy and safety.

Very likely, the major drawback would be the psychoactive effects, which, while sought out by those who use marijuana socially, are unwanted effects when the drug is used therapeutically. This difficulty might be met if one could find a cannabinoid that retained the antiemetic action without causing any mental changes. As isomer of the synthetic cannabinoid, 7-hydroxy-delta-6-tetrahydrocannabinol, is devoid of psychoactivity. Yet, in pigeons treated with the anticancer drug cisplatin, a drug most likely to cause vomiting, it showed antiemetic effects (Feigenbaum et al. 1989). Thus, the goal of separating these effects may be within reach. However, the number of drugs now shown useful for control of vomiting has increased greatly since cannabinoids were first considered as useful. The issue may have become

moot, unless such cost considerations prevail more in the future than they have in the past.

Appetite Stimulation

Frequent anecdotal reports by users of cannabis testify to the development of a ravenous appetite with a craving for sweets, especially chocolate. An experimental study, using a standardized chocolate milkshake, tested this idea. Subjects were treated with oral doses of THC 0.5 mk/kg, as well as placebo, alcohol and dextroamphetamine as a negative control. Of 12 fasted subjects, 7 who received THC increased their intake, 2 showed no change and three consumed less as compared with placebo. As expected, dextroamphetamine decreased intake. Alcohol, despite the calories provided, produced little change. When 12 subjects were fed before the test, 7 increased food intake, and 5 showed no change. Results were inconstant, both within and between subjects (Hollister 1971).

After 21 days of inpatient marijuana smoking, both body weight gain and caloric consumption were higher in casual and heavy users than in the control subjects (Greenberg et al. 1976). The psychological toxicological effects of chronic administration (0.1-0.34 mg/kg po qid) of THC were studied in cancer patients on in-and-out patient bases. The clinical observations demonstrated that THC slows or reverses weight loss and possesses some antiemetic and analgesic properties (Regelson et al. 1976).

The wasting syndrome associated with AIDS has made the search for drugs that might stimulate appetite more meaningful. THC in the form of dronabinol has been most often studied. An open pilot study of dronabinol in patients with AIDS-associated cachexia showed it effective in increasing weight as well as being well tolerated. Ten men received doses of 2.5 mg three times daily for periods of 4 to 20 weeks. Eight patients gained weight an average of 0.6 kg/month while 2 showed no gain. Initially, patients had been losing weight at the rate of 0.93 kg/month. Increasing the dose to 5 mg three times daily did not enhance weight gain (Plasse 1991).

A randomized double-blind comparison of dronabinol 2.5 mg twice daily with placebo over a 6 week period was completed in 88 patients. Before the study, patients were at least 2.3 kg below their ideal weight. Among the dronobinol-treated patients, the mean weight gain was 0.1 kg from baseline compared with a loss of 0.4 kg among the placebo

group. Side effects were not severe enough to merit discontinuation of treatment (Beal et al. 1995). Following the controlled study, patients entered an open study of one year's duration. Doses could vary between 2.5 and 20 mg/day according to response. A weight gain of 2 kg was found in those patients who completed three months of treatment. No evidence of the development of tolerance was noted. Side effects were not a major problem.

A phase 2 study of dronabinol in patients with cancer-associated anorexia and weight loss, revealed that low doses (2.5 mg twice daily after meals) improved appetite. Despite the low dose, 22% of patients withdrew from therapy because of side effects (Nelson et al. 1994). In a letter concerning this subject, the authors responded that dronabinol was safe and effective for appetite stimulation during chemotherapy, but that they considered metoclopramide, megestrol and dexamethasone better (Nelson and Walsh 1995). As the latter drugs are mainly used as antiemetics, one wonders whether whatever weight gain they might have provided was due to that action.

Four studies explored the role of age, gender, satiety state, and route of drug administration and dose on appetite stimulation in normal men. Increased food intake was found only after chronic dosing with rectally administered THC 2.5 mg three times daily for 3 days. Orally administered THC in the same dose did not increase appetite. Nor did inhalation of marijuana smoke. The conclusion was that appetite stimulation from cannabinoids was highly variable (Mattes et al. 1994).

An experimental approach to determine the effect of marijuana smoking on appetite used 7 men who were sequestered during observation. A single marijuana cigarette smoked during a period of isolation and work had no effect. However, 2-3 cigarettes smoked during a period of socialization increased caloric intake. The intake was largely in the form of snacks rather than increased consumption at mealtime (Foltin et al. 1986).

Testosterone enanthate, a long-acting injectable form, given in doses of 200 mg IM every 3 weeks, increased weight gain in AIDS patients, most particularly in the form of increased lean body mass. It should be noted that all these patients showed a low serum testosterone level at baseline, which may limit this beneficial effect to such patients (Grinspoon et al. 1998). Nonetheless, testosterone, other anabolic steroids, and human growth hormone might be reasonable competitors of THC for this indication.

Spasticity

It is said around our hospital if you want to know what marijuana smoke smells like, you should drop by the spinal cord injury ward. Such patients think that marijuana is helpful for relieving the pain and muscle spasm secondary to spinal cord injuries.

Ten patients who admitted using marijuana after spinal cord injury perceived a decrease in pain and spasticity as reported on a questionnaire (Dunn and Davis 1974). Another questionnaire given to 43 patients also with spinal cord injury reported decreased spasticity following marijuana use. Current use was related to past use and to use by peers, suggesting some possible bias in reporting (Hanigan et al. 1986).

The effects of oral THC 35 mg/day on muscle resistance, deep tendon reflexes and spasticity was evaluated in 5 patients with traumatic paraplegia. Two patients showed beneficial effects of THC, two had no real benefit and the fifth withdrew from the study because of the mental side effects (Malec et al. 1990).

A double-blind study was performed comparing 5 mg of THC orally, 50 mg codeine orally, and placebo in a patient with spasticity and pain due to spinal cord injury. The three conditions were applied 18 times each in a randomized and balanced order. THC and codeine both had an analgesic effect in comparison with placebo. Only THC showed a significant beneficial effect on spasticity. In the dosage used, no altered consciousness occurred (Maurer et al. 1990).

An antispastic action of THC was confirmed by the first clinical study. Oral doses of 5 and 10 mg of THC were compared with placebo in patients multiple sclerosis. The 10 mg dose reduced spasticity by clinical measurement (Petro and Ellenberger 1989).

A short-term trial of oral THC in 13 patients with multiple sclerosis and spasticity refractory to standard drugs revealed that a dose of 7.5 mg/day was the minimally effective dose. At this dose, subjective spasticity scores were less for THC than placebo. However, on objective measurements, there were no differences. A dose of 7.5 g/day was also highest tolerated; none of the patients in the trial requested continuation after the blind condition was abandoned (Meinck et al. 1989). A study of one patient with multiple sclerosis and another with spinal cord injury showed that doses of 5 mg/day of THC produced some relief of symptoms. Improvement in a 30-year-old man with multiple

sclerosis after smoking a marijuana cigarette was confirmed by electromyography of the flexor muscles of the leg and measurement of hand action tremor (Ungerleider et al. 1987). Administration of oral THC 5 to 10 mg to eight severely disabled multiple sclerosis patients yielded mild subjective improvement in tremor and sense of well being among two patients (Clifford 1983). The overall impression is that THC has some beneficial effect on spasticity, but tolerance to the side effects of the drug may be idiosyncratic.

On the other hand, a group that started with the premise that marijuana would reduce the spasticity of patients with multiple sclerosis and permit better postural control found the opposite. Ten adult patients with that disease were compared with 10 normal volunteers after smoking a marijuana cigarette. Both groups suffered a decrease in posture and balance as measured by a computer-controlled dynamic posturographic platform. No differences were observed between them (Greenberg et al. 1994). The medical treatment of spasticity with drugs such as diazepam, cyclobenzaprine, baclofen and dantrolene leaves much to be desired. In this case, smoking marijuana, which produces a sudden rise of THC levels, might not be the best route of administration. Further studies with oral dosing are required before this indication is written off.

A questionnaire concerning the effects of marijuana in 122 patients with multiple sclerosis revealed a generally beneficial profile of perceived effects. In descending order, the following symptoms were reported as being relieved: spasticity (97%), chronic pain in extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue, double vision, sexual, bowel and bladder dysfunction, and visual dimness (30%). Thus, we are faced with a substantial conflict between patients' perceptions and objective studies (Consroe et al. 1997).

Cannabidiol, another naturally occurring cannabinoid, was given in doses increasing from 100 to 600 mg/day to five patients with idiopathic dystonias, along with previously administered treatments. Dose-related improvement ranging from 20% to 50% was noted in all patients. However, in two patients with coexisting Parkinson syndromes, doses of over 300 mg/day exacerbated the hypokinesia and resting tremor, indicating an aggravating action in such patients (Consroe et al. 1986).

Analgesic Effects

Preclinical evidence of an analgesic effect of cannabinoids is strong. THC and the synthetic homologues, nantradol, and nabilone, shared some properties with morphine in the chronic spinal dog model. Latency of the skin twitch reflex was increased, and withdrawal abstinence was suppressed. Naltrexone did not antagonize these actions, suggesting that they are not mediated through opiate receptors which might suggest the eventual combination of opiate and cannabinoids (Gilbert 1981).

Both THC and a synthetic cannabinoid induced an antinociceptive effect in spinally transected rats, indicating a supraspinal mechanism of analgesia. Previously the same investigators had found evidence of a spinal site mediated through spinal alpha-adrenergic receptors (Lichtman and Martin 1991).

There is clinical support for an analgesic action as well. Single oral doses of 10 mg and 20 mg of THC compared with codeine (60 mg and 120 mg) in patients with cancer pain. A 20 mg dose of THC was comparable to both doses of codeine. The 10 mg dose, which was better tolerated, was less effective than either dose of codeine (Noyes et al. 1975). THC given IV in doses of 44 ng/kg to patients undergoing dental extraction produced an analgesic effect, which was less than that achieved from intravenous doses of 157 μg of diazepam. Several of these patients actually preferred placebo to the dose of 22 μg of THC per kg because of anxiety and dysphoria from the latter drug (Raft et al. 1977). Intramuscular levonantradol was compared with placebo in postoperative pain, and a significant analgesic action was confirmed. No dose-response relationship was observed, and the number of side effects from levonantradol was rather high (Jain et al. 1981).

Paradoxically, smoking of material estimated to deliver 12 mg of THC increased sensitivity to an electric shock applied to the skin of normal volunteers (Hill et al. 1974). The apparent paradox is that the biphasic action of THC (initial stimulation followed by sedation) both increases and decreases pain. Traditionally, aspirin-like drugs, which work peripherally by inhibiting the synthesis of prostaglandins, are used to treat pain derived from the integument. The initial mental stimulation from THC might increase sensitivity to this kind of pain. Visceral pain, such as that of cancer patients, is usually treated by

opiates having both peripheral and central sites of action. Recent evidence suggests that opiates may act directly on pain pathways in the spinal cord as well as reducing the affective response that accompanies pain. Thus, when the two types of pain are distinguished from each other and viewed in the context of the sequential biphasic action the apparent paradox is solved.

Because THC and other cannabinoids seem to be relatively safe (no deaths from overdose) and produce at best only a mild form of dependence, the notion of producing a synthetic cannabinoid with few other actions than analgesia has stimulated a great deal of interest on the part of various pharmaceutical companies. While it seems unlikely that THC itself will ever be used as an analgesic, synthetics may ultimately fulfill this role. Such drugs might be expected to act primarily on peripheral cannabinoid receptors rather than on those abundant in the CNS.

INDICATIONS WITH SPARSE EVIDENCE OF EFFICACY

Glaucoma

Discovery of the ability of cannabis to lower intraocular pressure (IOP) was more or less fortuitous. Intraocular pressure was measured as part of a multifaceted study of the effects of chronic smoking of large amounts of cannabis. IOP was found to decrease as much as 45% in 9 of 11 subjects, 30 min after smoking (Hepler and Frank 1971). Lowered intraocular pressure lasted 4 to 5 h after smoking a single cigarette. Its magnitude was unrelated to the total number of cigarettes smoked. The maximal effect on IOP was produced by the amount of THC absorbed in a single cigarette containing 19 mg of THC. When patients with ocular hypertension or glaucoma were tested, 7 of 11 showed a fall of intraocular pressure of 30%. Confirmatory evidence was obtained from a trial in which intravenous injection of THC in doses of 22 μg/kg and 44 μg/kg produced an average fall in IOP of 37%, with some decreases as much as 51% (Cooler and Gregg 1977).

The effects of intravenously administered cannabinoids on IOP were measured in 12 normal volunteers. Half received intravenous doses of THC, cannabidiol and cannabinol, the other half received doses of delta-8-THC, 11-hydroxy-THC, and 8-beta-hydroxy-del-

ta-9-THC. Total dose of THC and its 11-hydroxy metabolite was 3 mg; delta-8-THC was given in total dose of 6 mg, 8-beta-hydroxy-THC to a total of 9 mg, cannabinol and cannabidiol to total of 20 mg. Significant reductions in IOP were produced by the THC, delta-8-THC, and 11-hydroxy-THC, all of which are psychoactive compounds while the other cannabinoids had little or no such activity. Thus, it seemed impossible to separate mental effects, which were considerable for the effective drugs, from lowering of IOP (Perez-Reyes et al. 1976).

Orally administered THC (20 or 25 mg) lowered IOP about 8 mm Hg among 17 patients with heterologous glaucomas. No such lowering was found in patients who received only 5 or 10 mg doses. All patients who received the higher doses experienced severe mental effects. One patient, who received only a 5 mg dose, experienced severe tachycardia and orthostatic hypotension (Merritt et al. 1980).

Similar findings were reported from the same group after having 16 patients smoke marijuana cigarettes weighing 900 mg (amount of THC unspecified). Compared with placebo, IOP was lowered for 3-4 hours following the smoke. However, rapid heart rate and lowering of blood pressure which preceded this action were quite large and would not be tolerated by many patients among the age group who suffer glaucoma (Merritt et al. 1980).

As treatment for glaucoma is a lifetime proposition, systemic therapy has never been seriously considered. Topical therapy, properly used, has been generally satisfactory. Unfortunately, attempts to make a tolerable topical preparation of THC or other cannabinoids have been impossible to date. One hears tales of patients with glaucoma whose vision is spared only by smoking marijuana cigarettes; remarkably, no case reports, along with objective measurements, even of a few such patients, have appeared. As glaucoma occurs most often in older patients, one has difficulty imagining such patients embracing a lifetime of possible marijuana intoxication. This possible indication has elicited no literature during the past 12 years.

Anticonvulsant

One of the therapeutic uses suggested for cannabis was as an anticonvulsant. Such an effect was documented experimentally many years ago (Loewe and Goodman 1947). Studies in various animal species have shown cannabidiol effective in many animal-screening tests for anticonvulsants (Wada et al. 1973; Turkanis et al. 1974).

Clinical testing has been rare, despite all these various lines of evidence supporting an anticonvulsant effect of cannabinoids. Better control of seizures following regular marijuana smoking was reported in a not very convincing single case (Consroe et al. 1975).

Cannabidiol (CBD), a non-psychoactive cannabinoid, was tested in 15 epileptic patients poorly controlled by usual drugs. Patients were randomly assigned to a dose of 300 mg of CBD or placebo and treated for as long as 4 1/2 months, while continuing their past anticonvulsant drugs. Of 8 CBD-treated patients, 4 remained free of seizures, 3 showed partial improvements and 1 showed no response. Of 7 placebo-treated patients, only 1 showed improvement. The drug was well tolerated (Cunha et al. 1980). As cannabidiol has little if any psychoactivity, it is a good candidate for this use.

The number of effective anticonvulsants has increased since the original interest in cannabidiol. Consequently, no further clinical studies have been reported.

Bronchial Asthma

A general study of the effects of marijuana on respiration revealed a bronchodilating action in normal volunteer subjects. Marijuana smoke delivered by smoking cigarettes containing 2.6% THC caused fall of 38% in airway resistance and an increase of 44% in airway conductance, with less change when a 1% THC cigarette was smoked. The low-dose group showed lesser changes, but they were still significant as compared with baseline (Vachon et al. 1973).

Asthma was deliberately induced by either inhalation or methacholine or exercise in asthmatic patients. They were then treated with inhalation of placebo marijuana, of saline, of isoproterenol, or of smoke derived from 500 mg of marijuana containing 2% THC. Both marijuana smoke and isoproterenol aerosol effectively reversed both methacholine- and exercise-induced asthma while saline and placebo marijuana had no effect (Tashkin et al. 1975).

Aerosols of placebo-ethanol, THC (200 μg) in ethanol, or of salbutamol (100 μg) were tested in another study of 10 stable asthmatic patients. Forced expiratory volume in 1 s, forced vital capacity, and peak flow rates were measured on each occasion. Both salbutamol and THC significantly improved ventilatory function. Improvement was more rapid with salbutamol, but two treatments were equally effective at the end of 1 h (Williams et al. 1972).

While it is conceivable that an aerosol preparation could be made, those currently used (corticosteroids and beta-adrenergic agonists) are well established. Although treatment of asthma in the past has employed smoked drugs (stramonium [*Datura* spp.] cigarettes known as cubebs were used until 60-70 years ago), it seems intuitively wrong to treat a pulmonary condition with a method of drug administration that increases inflammation. As treatment of bronchial asthma has shifted towards emphasis on alleviating the inflammatory aspects, there is little support for using smoked marijuana. Consequently, interest in the indication is currently non-existent.

Insomnia

THC does not differ from conventional hypnotics in reducing rapid eye movement (REM) sleep (Pivik et al. 1972). THC in doses ranging from 61 to 258 μg/kg produces in normal subjects increments in stage four sleep and decrements in REM sleep, but without the characteristic REM rebound which follows chronic treatment with an hypnotic. When THC was administered orally as a hydroalcoholic solution in doses of 10, 20, and 30 mg, subjects fell asleep faster after having mood alterations consistent with a "high." Some degree of "hangover" the day following was noted from larger doses (Cousens and Dimascio 1973). Another sleep laboratory study showed that a dose of 2 mg of THC given orally decreased REM sleep. After 4-6 nights of use, abrupt discontinuation of THC produced a mild insomnia but not marked REM rebound (Freemon 1974). REM rebound may not be apparent after low doses of THC; however, very high doses (70 to 210 mg) reduced REM sleep during treatment and were followed by marked REM rebound after withdrawal (Feinberg et al. 1976). The sleep produced by THC does not seem to differ much from that of most currently used hypnotics. Side effects before sleep induction as well as hangover effects make the drug less acceptable than currently popular benzodiazepines. No further studies have been reported.

Early on, synthetic cannabinoids were tried as antianxiety and antidepressant drugs. Diazepam 5 mg was superior to the synthetic cannabinoid nabilone 2 mg for treating experimentally induced anxiety in highly anxious people. Thus, even aside from the marijuana-like effects of nabilone, it was not acceptable (Nakano et al. 1978). Following a favorable report from use of synexyl for treatment of depression, a further study found it to be of no benefit (Parker and Wrigley 1950).

Again, cannabinoid-like drugs were of little use in these psychiatric conditions. Nor has there been any attempt to exploit them in this fashion over the succeeding decades.

DISCUSSION

Among the many possible therapeutic uses of marijuana, a few have enough supporting evidence to justify further studies. Greatest support has been elicited for using the drug, mainly in the form of orally administered THC, for the control of nausea and vomiting. This use has been further legalized by the switch of synthetic oral THC to Schedule III of the Controlled Substances Act. Capsules (Marinol® or dronabinol) containing THC dissolved in oil have been marketed for this purpose. Demand for such preparations has not been great, however, probably because of the reluctance of physicians to prescribe a drug that so recently was considered illegal and possibly also to the fact that many other antiemetics have been developed during the past decade which obviate the mental side effects of THC. The remaining issue is whether smoked marijuana might be superior, as such administration permits rapid and close titration of dose. This issue has not been resolved and would take a large, expensive clinical trial to settle. Thus far, no support has been offered for such a trial.

As appetite stimulants are not very effective, this possible action of marijuana is certainly worth consideration. Data suggest that stimulation is inconstant and mild. All of the studies have involved oral THC, which would seem to be the most appropriate route for this purpose, its slower but more prolonged duration of action being consonant with the aims of treatment. Anabolic steroids offer another approach to this indication. Comparisons between these and THC would be required.

Available medications to relieve muscle spasticity are generally somewhat disappointing. Whether the few reports of benefit from marijuana improve the situation is questionable. The incoordinating effects of this drug might aggravate the underlying neurological condition.

Development of cannabinoids as analgesics is attractive, but it seems obvious that neither oral THC nor smoked marijuana is the best approach. If synthetic cannabinoids could be developed which retain the analgesic action but minimize the mental effects, this indication would be more promising.

Other potential medical uses, such as treatment for glaucoma, asthma, seizures and insomnia or anxiety, not only have very little experimental support but also would seem adequately treated with existing drugs. During the past dozen years, little interest in exploring these is apparent in the medical literature.

A major unresolved issue is the comparison between orally administered THC and smoked marijuana. Many users aver that smoke marijuana may have active ingredients other than THC, as perhaps 300 or so chemicals are present in the plant or in the smoke. As few of these have ever been studied alone (nor will they be), the argument cannot be settled directly. On the other hand, except for some THC-like structures, which are present in marijuana in much smaller amounts, and with far less potency than that of THC, no other active material has been found. Thus, it appears unlikely that some panacea is being missed. As for the kinetic advantages of smoking, immediate effects might be desirable for situations in which immediate action is preferable; most drugs are used for longer-lived conditions in which sustained effects are more essential.

CONCLUSION

It is surprising that more than 35 years after the synthesis of THC, and the resulting capability of clinical pharmacological studies, little published literature has tested various potential therapeutic uses of the drug. Earliest studies were more concerned with the actions of the drug on various organ systems and were not concerned with therapeutic actions. For part of the past 15 years, an increasing literature explored this aspect but has recently dropped off. Therapeutic use has become entwined with the political and legal moves that have polarized investigators. The consequence is that legal steps have been taken which are poorly supported by medical evidence.

For those of us who like to have new treatments accepted on the basis of evidence rather than plebiscite, it has been a discouraging period. The solutions proposed by the recent Institute of Medicine Report would seem to be even more discouraging than those which were obtained before. In view of the fact that marijuana and its constituents may be among the safest materials one can be exposed to, it would seem reasonable to make its testing less, rather than more difficult.

Meanwhile, we must ponder the question, "Are we missing a therapeutic advance or is the lore of the past only folklore that has no place in modern science?" Innovation is desperately needed if we are to settle the question before all chances for proper appraisals are lost.

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Effects of Smoked Cannabis and Oral Δ^9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials

Richard E. Musty
Rita Rossi

ABSTRACT. Background. In 1999 the Institute of Medicine (IOM) issued a report entitled *Marijuana and Medicine* (Joy, Watson and Benson, 1999). It recommended the development of cannabinoid drug delivery systems which might be effective for nausea, vomiting and AIDS wasting syndrome, among other chronic disorders. The report went on to recognize that patients should be allowed to smoke marijuana if they failed to achieve relief from approved symptoms that could be relieved by cannabinoid drugs with rapid onset. Recommended criteria of the report included: access to marijuana within 24 hours of submission by a physician, supervision that allows for assessment of treatment effectiveness, and an oversight strategy comparable to an institutional review board. In this context a review of previously unpublished state-run clinical trials with *Cannabis sativa* (marijuana and/or Δ^9-tetrahydrocannabinol capsules) to test efficacy in reducing nausea and vomiting following cancer chemotherapy is warranted. The impetus for these studies came from individual state legislatures responding to constituents' claims that smoking marijuana reduced or blocked nausea and vomiting.

Methods. Technical reports were obtained from 6 states which had

Richard E. Musty, PhD, and Rita Rossi are affiliated with the Department of Psychology, University of Vermont, Burlington, VT 05405.

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conducted clinical trials. Each protocol was examined for the procedure used, the experimental design of the clinical trial and the results obtained. Data were available on 748 patients who smoked marijuana prior to and/or after cancer chemotherapy and 345 patients who used the oral THC capsule.

Results. Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief.

Conclusions. On the basis of these studies, it appears that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy.

The development of smokeless inhalation devices could certainly reduce the potential harm from smoking marijuana.

KEYWORDS. Cannabis, cannabinoid, marijuana, cancer, chemotherapy, nausea, vomiting, tetrahydrocannabinol

The first study comparing oral Δ^9-tetrahydrocannabinol (THC) to placebo capsules and marijuana to marijuana placebo cigarettes was published by Chang et al. (1979). In this study 15 patients were given oral doses of THC over several courses of chemotherapy. Each subject received a 10 mg THC capsule beginning two hours prior to chemotherapy and every three hours subsequently. In the event of a breakthrough vomiting episode, those patients were given marijuana cigarettes to smoke for the remaining administrations rather than oral THC. When measured THC blood levels were < 5 ng/ml, 44% of subjects vomited, between 5 ng/ml and 10 ng/ml, 21% vomited, and > 10 ng/ml, 6% vomited. After smoking marijuana, the incidence of vomiting for the same blood levels ranges were 83%, 38% and 0%. Vomiting rates after placebo capsules or smoked placebo marijuana were 72% and 96%, respectively.

In a marijuana-only trial, Vinciguerra et al. (1988) tested 56 patients, non-randomized, who acted as their own controls. Patients rated themselves via subjective assessment of nausea and vomiting. Thirty-four percent of the patients rated smoked marijuana as being very effective, 44% moderately effective, and 22% ineffective. The authors did not report the frequency of nausea and vomiting when marijuana was not smoked.

Technical reports were obtained from 6 states, in which inhaled marijuana was used in patients undergoing cancer chemotherapy. The states had passed legislation to make these studies legal. Usually, studies were designed by researchers in collaboration with State Departments of Health. Each state was required to write a protocol for the research (which was submitted to the Food and Drug Administration (FDA) for approval). Subsequently, a Schedule I license was obtained from the Drug Enforcement Administration (DEA). Finally, rolled marijuana cigarettes and capsules of THC (in sesame oil) were obtained from the National Institute on Drug Abuse (NIDA). These studies will be reviewed individually in this article.

In 1999, the Institute of Medicine (IOM) recommended that marijuana be made available for patients refractory to other medications (Joy, Watson and Benson, 1999). This review provides further support to the Chang and Vinciguerra studies.

TENNESSEE

Background. The State of Tennessee conducted this trial after legislative action in April of 1981 (Board of Pharmacy, 1983).

Treatment Method. Patients (all of whom were refractory to other anti-emetics) were referred for treatment by the patient's personal physician. Patient records were reviewed by a Patient Qualification Review Board of the State of Tennessee. Those approved were randomized to 3 age groups: less than 20 years old, 20-40 years old, and over 40 years old. Those not having conditions precluding oral administration were administered the THC capsule and those unable to ingest capsules were treated with smoked marijuana cigarettes. Most of the patients had previously been treated with the THC capsule. Thus the report focused on the effects of use of marijuana cigarettes.

Measures. A patient treatment evaluation form was completed for each day of treatment. Recording forms included a record of dose and notes, the patient's assessment of nausea and vomiting, appetite and food intake, physical state, and (marijuana) "high." Forty-three patients were enrolled in the study. Sixteen patients were excluded for various reasons: missing data, abusive drug use, premature death, those who could not tolerate smoking, or patients who declined treatment.

Results. The results of the study are shown in Table 1. Treatment

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success by method was also discussed. Success was defined as partially, moderately, or very effective. For those under age 40 years of age, 100% success was achieved with marijuana cigarettes. For those over 40, 83.3% success was achieved. Only 6 patients used the THC capsule alone and 100% success occurred in those under 40 years of age, and in 33% for those over 40. Side effects were predominantly mild, and appetite improved in about 1 out of 5 patients.

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Background. Michigan conducted a study under the direction of the Michigan Department of Public Health after legislative action in 1979. John. R. Ingall of the Detroit Metropolitan Comprehensive Cancer Center was the study coordinator, and the report was complied by the Michigan Cancer Foundation (Department of Social Oncology, Evaluation Unit 1982).

Treatment Method. In order to be eligible for the trial, patients had to meet these criteria: be under active cancer chemotherapy treatment, have a satisfactory medical status such that potential side effects of marijuana or a phenothiazine derivative, thiethylperazine (Torecan®), were not life-threatening or likely to evoke serious mental/behavioral effects, and be free of serious mental or organic disease. Patients were randomly assigned to a marijuana cigarette or thiethylperazine therapy group. If the treatment failed in a 24 hour trial, patients were then crossed over to the other treatment group. For the marijuana group,

patients took one puff per minute until they felt "high" 30 minutes prior to chemotherapy. The smoking procedure continued until sometime after chemotherapy was completed. One hundred sixty-five patients completed this trial (78 male and 86 female).

Measures. Measures were recorded by patient self-report as well as physician/nurse observations.

Results. The results for this study are shown in Table 2. Marijuana was marginally more effective as compared to thiethylperazine in controlling nausea and vomiting/retching. As in the previous study, reported side effects were mild.

GEORGIA

Background. The State of Georgia and Emory University collaborated to conduct this trial after legislative action in 1980 (Kutner 1983).

Treatment Method. Cancer patients who were unresponsive to usual anti-emetics, but who were able to employ the oral route of administration were eligible for this trial. Patients were randomly assigned to one

TABLE 2. Michigan Trial: Frequency of Nausea, Vomiting/Retching and Side Effects

	Nausea		Vomiting/Retching After Chemotherapy		
	Marijuana	Torecan*		Marijuana	Torecan*
None	14 (15.0%)	8 (15.7%)	None	19 (18.1%)	10 (14.9%)
Mild	31 (33.3%)	16 (31.4%)	Less than 4 h	25 (23.8%)	19 (28.4%)
Moderate	22 (23.7%)	14 (27.5%)	Between 4-12 h	25 (23.8%)	19 (28.4%)
Severe	19 (20%)	12 (23.5%)	Between 12-24 h	14 (13.3%)	10 (14.9%)
Unknown	7 (7.5%)	1 (0.02%)	Over 24 h	9 (8.6%)	4 (6.0%)
			Unknown	13 (12.4%)	5 (7.5%)

Side Effects of Marijuana Smoking	
Sleepiness	21/113 (18.5%)
Sore Throat	13/113 (11.5%)
Headache	7/113 (6.2%)

* Thiethylperazine (Torecan®)

of three treatment groups by age: less than 20 years old, 20-40 years old, and over 40. The treatment groups were: oral THC capsules, standardized cannabis smoking, or patient controlled smoking.

Measures. At each treatment a form was completed containing information on effectiveness of treatment, side effects and the patient's assessment of nausea, vomiting, appetite, physical status, mood and "high." One hundred nineteen patients completed the study.

Observations included patient self-reports and physician summaries. Patient satisfaction was assessed for each treatment. Success was judged by the patient reporting as to whether he/she was satisfied, or very satisfied with the treatment. If the patient was not sure of effectiveness on the first cycle of treatment, but was satisfied or very satisfied on subsequent cycles, this was also considered to be a success. Failure was defined when the patient was dissatisfied on the initial cycle, the patient dropped out of the study, or changed treatment method.

Results. The overall results are shown in Table 3 and by age group in Table 4. Examining the data (in percentages) by age groups reveals success rates were very similar across age groups. These data show success rates were about the same for oral THC and patient controlled

TABLE 3. Georgia Trial: Overall Success with All Treatments by Age

	Age			
	< 20	20-40	> 40	Total
Success	10 (71.4%)	30 (75%)	47 (72.3%)	87 (73.1%)
Failure	4 (28.6%)	10 (25%)	18 (27.7%)	32 (26.9%)
Total	14	40	65	119

TABLE 4. Georgia Trial: Success by Treatment Oral THC (PO), Standardized Smoking (SS) and Patient Controlled Smoking (PCS) of Marijuana

	PO	SS	PCS	Total
Success	57 (76%)	17 (65.4%)	13 (72.2%)	87 (73.1%)
Failure	18 (24%)	9 (34.6%)	5 (27.8%)	32 (26.9%)
Total	14	40	65	119

smoking, but standardized smoking yielded somewhat inferior outcomes.

Reasons for failure in patients who failed treatment with oral THC were as follows: 8 patients experienced severe nausea and vomiting, 6 had adverse reactions, 2 were dissatisfied, 1 had breakthrough vomiting, and 1 had no effect. For those who smoked marijuana, 6 patients experienced smoking intolerance, 1 had an adverse reaction, 1 had severe nausea and vomiting, 2 had breakthrough vomiting, and 4 had other side effects.

NEW MEXICO (1983)

Background. This program of Research was conducted by the Lynn Pierson Therapeutic Research Program for the New Mexico Health and Environment Department after authorization by the legislature in 1978 (Behavioral Science Division, 1983).

Treatment Method. Patients enrolled in the program were randomly assigned to one of two treatments: THC capsule or marijuana cigarettes. Doses were matched so that each patient received approximately 15 mg of THC. Patients were administered the treatment before a cycle of chemotherapy. After chemotherapy, patients could continue taking the marijuana or THC for 5 days. Forty female patients and 27 male patients received marijuana cigarettes, while 50 female patients and 25 male patients received THC capsules.

Measures. Observations were made by patients with a self-report scale called the Target Problem Rating Scale. For nausea and vomiting, improvement was defined when patients reported less nausea or vomiting compared with previous anti-emetics. No improvement was defined as no change compared with previous anti-emetics.

Results. The data are shown in Table 5. Patients who smoked marijuana achieved improvement overprevious antiemetic drugs, with those smoking the drug exceeding 90% success.

TABLE 5. New Mexico Trial (1983)

Group	Oral THC	Inhaled Marijuana
Improvement	57 (74.83%)	58 (90.39%)
No Improvement	9 (25.17%)	3 (9.6%)

NEW MEXICO (1984)

Background. The Lynn Pierson Therapeutic Research Program continued in 1984 (Behavioral Science Division 1984).

Treatment Method. The program was similar to that in 1983, with the exception that some patients received only one treatment and others received an average of six treatments after chemotherapy. Patients were randomly assigned to the same treatment groups as in the 1983 protocol. The protocol also allowed patients options to begin in one treatment group and switch to another, to refuse to be in the smoking group, or to try both routes of administration sequentially. Success was defined as a reduction in nausea and vomiting, and failure was defined as no reduction. Table 6 shows the results. It is important to note that few patients continued with the oral THC treatment, while those who smoked marijuana achieved over 90% success. Summarizing side effects of both THC and marijuana reported over the two years, treated patients often fell asleep. Of those who did not (approximately 90 patients), 50% reported sleepiness and 45% felt "high." No other side effects were noted in the report.

CALIFORNIA

Background. After legislation passed by the State of California Legislature in 1979, a Cannabis Therapeutic Program was carried out between 1983 and 1989 under the supervision of the California Research Advisory Panel (1989).

Treatment Method. Over the years, several protocols were used. Essentially, the early protocols were conservative, e.g., patients were required to have failed treatment with conventional anti-emetic drugs. Later, a more relaxed protocol was used in which the patient and the physician decided whether or not to try the THC capsule or smoke marijuana.

TABLE 6. New Mexico Trial (1984): Treatment Success After the First Treatment with Inhaled Marijuana or Oral THC

Group	Oral THC	Inhaled Marijuana	Combined
Success	6 (54.5%)	79 (95.2%)	79 (98.8%)
Failure	5 (45.5%)	4 (4.8%)	1 (1.2%)

Measures. Physicians used 5 point rating scales to record nausea and vomiting.

Results. Table 7 shows the combined results of the various protocols combined. In this study, smoked marijuana was consistently more effective than oral THC in blocking vomiting except in the most severe cases (> 6 times). Control of nausea was about the same for both groups. The pattern of side effects did not differ, to any extent, between smoked marijuana and oral THC.

NEW YORK

Background. The New York Department of Health study conducted a large scale (Phase III type) cooperative clinical trial (Randall, 1990).

Treatment Method. The central question addressed was how effective inhaled marijuana was in preventing nausea and vomiting due to chemotherapy in patients who failed to respond to previous anti-emetic therapy. Patients undergoing chemotherapy were allowed to use marijuana distributed through three centers: North Shore Hospital (NSH), Columbia Memorial Hospital (CMH), and a triad of the Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital (JGH). By 1985, the New York program provided marijuana therapy to 208 patients through 55 practitioners. Of those, data on 199 patients were evaluated. These patients had received a total of 6,044 NIDA-

TABLE 7. California Trials: Ratings of Nausea and Vomiting for Smoked Marijuana or the THC Capsule.

	Smoked Marijuana	THC Capsule		Smoked Marijuana	THC Capsule
Nausea			Vomiting		
None	9 (9.2%)	38 (15.1%)	None	19 (19.4%)	89 (35.3%)
Mild	34 (34.7%)	85 (33.9%)	1-3 times	36 (36.7%)	69 (27.4%)
Moderate	36 (36.7%)	73 (29.1%)	4-6 times	18 (18.4%)	35 (13.9%)
Severe	17 (17.3%)	55 (21.9%)	> 6 times	24 (24.5%)	59 (23.4%)
Missing	2 (2%)	6 (2.3%)	Missing	1 (1%)	5 (2.3%)

Side Effects (combined ratings from mild to severe are shown Table 8).

TABLE 8. California Trials: Side Effects Reported by Patients

	Smoked Marijuana n = 98	Smoked Marijuana %	THC Alone n = 257	THC Alone %
Dry Mouth	53	56.5	112	44.8
Tachycardia	6	6.4	25	10.0
Ataxia	16	27.1	31	12.8
Dizziness	31	33.1	67	26.8
Orthostatic	7	7.5	32	12.8
Anxiety	19	20.2	47	18.8
Sedation	49	52.1	160	64.0
Elated Mood	25	26.6	61	24.4
Confusion	23	26.6	79	31.6
Perceptual	15	15.9	57	22.8
Fantasizing	10	10.7	29	11.6
Depressed	17	18.1	33	13.2
Panic/Fear	7	7.5	9	7.6

supplied marijuana cigarettes provided to patients during 514 treatment episodes.

Measures. Observations were made by patient self-report.

Results. North Shore Hospital reported marijuana was effective at reducing emesis 92.9% of the time; Columbia Memorial Hospital reported efficacy of 89.7%; the triad of Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital reported 100% of the patients smoking marijuana gained significant benefit.

Analyzing patient evaluations, the report concluded that approximately 93% of marijuana inhalation treatment episodes were effective or highly effective when compared with other anti-emetics. The New York study reported no serious adverse side effects. No patient receiving marijuana required hospitalization or any other form of medical intervention.

DISCUSSION

Even though slightly different methods and different research designs were used in these studies, it is clear that inhaled marijuana was

effective in reducing or eliminating nausea and vomiting following cancer chemotherapy. In those studies which compared the inhalation route to oral THC, inhalation was equal to or better than oral administration. In almost all of these studies, patients were admitted only after they failed treatment with standard anti-emetics, suggesting the patients may have been under fairly aggressive treatment for their cancers.

With regard to side effects, short term use of marijuana leads to sedation, a high, and smoke intolerance in some patients. At this point in time there is no conclusive evidence that marijuana smoke seriously affects the immune system or is associated with cancer (Joy, Watson and Benson, 1999).

In a 1991 survey, Doblin and Kleiman (1991) reported that more than 70% responding oncologists (n = 1035) reported at least one of their patients had used marijuana as an anti-emetic, and that they had also either observed or discussed the patients' use. In addition, 44% of the respondents reported recommending marijuana to at least one patient. Two hundred seventy-seven respondents felt they had clinical experience with both marijuana and Marinol™ (oral THC): (44% thought marijuana was more effective, 43% thought they were about equally effective, and 13% thought Marinol™ was more effective). These data suggest that physicians at that time continued to discuss or recommend marijuana use to some patients. In this sample of oncologists, it seems they understood the potential efficacy of marijuana use. Whether this situation has changed since 1991 is unknown, but one might argue that the introduction of the anti-emetics of the selective serotonin-3 antagonist class, may have changed this practice.

While there have been no studies which have compared smoked marijuana or Marinol™ with the serotonin receptor type-3 antagonists (granisetron or ondansetron), it is instructive to review published clinical trials with these compounds for the sake of comparison. In 9 clinical trials with ondansetron, anti-emesis was obtained in 40%-81% (mean 63.5%) of patients (Beck et al. 1993; Buser et al. 1993; Crucitt et al. 1994; Hainsworth et al. 1991; Herrstedt et al. 1993; Kaasa et al. 1990; Marty et al. 1980; Olver et al. 1996; Roila et al. 1991). In 5 clinical trials with granisetron, 37.7%-93% (mean 56.6%) anti-emesis was reported (Italian Group for Antiemetic Research 1995; Markman et al. 1996; Perez et al. 1997; Ritter Jr. et al. 1998; Sekine et al. 1996). It is generally known that combining anti-emetic drugs with different

mechanisms of action often improves efficacy (Jones et al. 1991). This suggests that future research should consider combining cannabinoids with other anti-emetics.

The data reviewed here suggest that the inhalation of THC appears to be more effective than the oral route. In order to achieve the IOM recommendation to allow patients access to marijuana, both state and Federal Governments would need to reschedule marijuana from Schedule I to Schedule II, or reinstate the Compassionate Use Program. The development of smokeless inhalation devices would certainly be an advance in the use of THC as an anti-emetic medication. Finally, a large number of synthetic cannabinoid and endocannabinoid agonist analogs have been developed. It would seem that testing of these compounds as potential anti-emetics would also be worthwhile.

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Effects of Smoked Cannabis and Oral Δ^9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials

Richard E. Musty
Rita Rossi

ABSTRACT. Background. In 1999 the Institute of Medicine (IOM) issued a report entitled *Marijuana and Medicine* (Joy, Watson and Benson, 1999). It recommended the development of cannabinoid drug delivery systems which might be effective for nausea, vomiting and AIDS wasting syndrome, among other chronic disorders. The report went on to recognize that patients should be allowed to smoke marijuana if they failed to achieve relief from approved symptoms that could be relieved by cannabinoid drugs with rapid onset. Recommended criteria of the report included: access to marijuana within 24 hours of submission by a physician, supervision that allows for assessment of treatment effectiveness, and an oversight strategy comparable to an institutional review board. In this context a review of previously unpublished state-run clinical trials with *Cannabis sativa* (marijuana and/or Δ^9-tetrahydrocannabinol capsules) to test efficacy in reducing nausea and vomiting following cancer chemotherapy is warranted. The impetus for these studies came from individual state legislatures responding to constituents' claims that smoking marijuana reduced or blocked nausea and vomiting.

Methods. Technical reports were obtained from 6 states which had conducted clinical trials. Each protocol was examined for the procedure used, the experimental design of the clinical trial and the results obtained. Data were available on 748 patients who smoked marijuana

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Richard E. Musty, PhD, and Rita Rossi are affiliated with the Department of Psychology, University of Vermont, Burlington, VT 05405.

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prior to and/or after cancer chemotherapy and 345 patients who used the oral THC capsule.

Results. Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief.

Conclusions. On the basis of these studies, it appears that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy.

The development of smokeless inhalation devices could certainly reduce the potential harm from smoking marijuana.

KEYWORDS. Cannabis, cannabinoid, marijuana, cancer, chemotherapy, nausea, vomiting, tetrahydrocannabinol

The first study comparing oral Δ^9-tetrahydrocannabinol (THC) to placebo capsules and marijuana to marijuana placebo cigarettes was published by Chang et al. (1979). In this study 15 patients were given oral doses of THC over several courses of chemotherapy. Each subject received a 10 mg THC capsule beginning two hours prior to chemotherapy and every three hours subsequently. In the event of a breakthrough vomiting episode, those patients were given marijuana cigarettes to smoke for the remaining administrations rather than oral THC. When measured THC blood levels were < 5 ng/ml, 44% of subjects vomited, between 5 ng/ml and 10 ng/ml, 21% vomited, and > 10 ng/ml, 6% vomited. After smoking marijuana, the incidence of vomiting for the same blood levels ranges were 83%, 38% and 0%. Vomiting rates after placebo capsules or smoked placebo marijuana were 72% and 96%, respectively.

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states had passed legislation to make these studies legal. Usually, studies were designed by researchers in collaboration with State Departments of Health. Each state was required to write a protocol for the research (which was submitted to the Food and Drug Administration (FDA) for approval). Subsequently, a Schedule I license was obtained from the Drug Enforcement Administration (DEA). Finally, rolled marijuana cigarettes and capsules of THC (in sesame oil) were obtained from the National Institute on Drug Abuse (NIDA). These studies will be reviewed individually in this article.

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Measures. A patient treatment evaluation form was completed for each day of treatment. Recording forms included a record of dose and notes, the patient's assessment of nausea and vomiting, appetite and food intake, physical state, and (marijuana) "high." Forty-three patients were enrolled in the study. Sixteen patients were excluded for various reasons: missing data, abusive drug use, premature death, those who could not tolerate smoking, or patients who declined treatment.

Results. The results of the study are shown in Table 1. Treatment success by method was also discussed. Success was defined as partially, moderately, or very effective. For those under age 40 years of age,

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100% success was achieved with marijuana cigarettes. For those over 40, 83.3% success was achieved. Only 6 patients used the THC capsule alone and 100% success occurred in those under 40 years of age, and in 33% for those over 40. Side effects were predominantly mild, and appetite improved in about 1 out of 5 patients.

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Measures. Measures were recorded by patient self-report as well as physician/nurse observations.

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Treatment Method. Cancer patients who were unresponsive to usual anti-emetics, but who were able to employ the oral route of administration were eligible for this trial. Patients were randomly assigned to one of three treatment groups by age: less than 20 years old, 20-40 years

TABLE 2. Michigan Trial: Frequency of Nausea, Vomiting/Retching and Side Effects

	Nausea		Vomiting/Retching After Chemotherapy		
	Marijuana	Torecan*		Marijuana	Torecan*
None	14 (15.0%)	8 (15.7%)	None	19 (18.1%)	10 (14.9%)
Mild	31 (33.3%)	16 (31.4%)	Less than 4 h	25 (23.8%)	19 (28.4%)
Moderate	22 (23.7%)	14 (27.5%)	Between 4-12 h	25 (23.8%)	19 (28.4%)
Severe	19 (20%)	12 (23.5%)	Between 12-24 h	14 (13.3%)	10 (14.9%)
Unknown	7 (7.5%)	1 (0.02%)	Over 24 h	9 (8.6%)	4 (6.0%)
			Unknown	13 (12.4%)	5 (7.5%)

Side Effects of Marijuana Smoking	
Sleepiness	21/113 (18.5%)
Sore Throat	13/113 (11.5%)
Headache	7/113 (6.2%)

* Thiethylperazine (Torecan®)

old, and over 40. The treatment groups were: oral THC capsules, standardized cannabis smoking, or patient controlled smoking.

Measures. At each treatment a form was completed containing information on effectiveness of treatment, side effects and the patient's assessment of nausea, vomiting, appetite, physical status, mood and "high." One hundred nineteen patients completed the study.

Observations included patient self-reports and physician summaries. Patient satisfaction was assessed for each treatment. Success was judged by the patient reporting as to whether he/she was satisfied, or very satisfied with the treatment. If the patient was not sure of effectiveness on the first cycle of treatment, but was satisfied or very satisfied on subsequent cycles, this was also considered to be a success. Failure was defined when the patient was dissatisfied on the initial cycle, the patient dropped out of the study, or changed treatment method.

Results. The overall results are shown in Table 3 and by age group in Table 4. Examining the data (in percentages) by age groups reveals success rates were very similar across age groups. These data show success rates were about the same for oral THC and patient controlled smoking, but standardized smoking yielded somewhat inferior outcomes.

TABLE 3. Georgia Trial: Overall Success with All Treatments by Age

	Age			
	< 20	20-40	> 40	Total
Success	10 (71.4%)	30 (75%)	47 (72.3%)	87 (73.1%)
Failure	4 (28.6%)	10 (25%)	18 (27.7%)	32 (26.9%)
Total	14	40	65	119

TABLE 4. Georgia Trial: Success by Treatment Oral THC (PO), Standardized Smoking (SS) and Patient Controlled Smoking (PCS) of Marijuana

	PO	SS	PCS	Total
Success	57 (76%)	17 (65.4%)	13 (72.2%)	87 (73.1%)
Failure	18 (24%)	9 (34.6%)	5 (27.8%)	32 (26.9%)
Total	14	40	65	119

Reasons for failure in patients who failed treatment with oral THC were as follows: 8 patients experienced severe nausea and vomiting, 6 had adverse reactions, 2 were dissatisfied, 1 had breakthrough vomiting, and 1 had no effect. For those who smoked marijuana, 6 patients experienced smoking intolerance, 1 had an adverse reaction, 1 had severe nausea and vomiting, 2 had breakthrough vomiting, and 4 had other side effects.

NEW MEXICO (1983)

Background. This program of Research was conducted by the Lynn Pierson Therapeutic Research Program for the New Mexico Health and Environment Department after authorization by the legislature in 1978 (Behavioral Science Division, 1983).

Treatment Method. Patients enrolled in the program were randomly assigned to one of two treatments: THC capsule or marijuana cigarettes. Doses were matched so that each patient received approximately 15 mg of THC. Patients were administered the treatment before a cycle of chemotherapy. After chemotherapy, patients could continue taking the marijuana or THC for 5 days. Forty female patients and 27 male patients received marijuana cigarettes, while 50 female patients and 25 male patients received THC capsules.

Measures. Observations were made by patients with a self-report scale called the Target Problem Rating Scale. For nausea and vomiting, improvement was defined when patients reported less nausea or vomiting compared with previous anti-emetics. No improvement was defined as no change compared with previous anti-emetics.

Results. The data are shown in Table 5. Patients who smoked marijuana achieved improvement overprevious antiemetic drugs, with those smoking the drug exceeding 90% success.

TABLE 5. New Mexico Trial (1983)

Group	Oral THC	Inhaled Marijuana
Improvement	57 (74.83%)	58 (90.39%)
No Improvement	9 (25.17%)	3 (9.6%)

NEW MEXICO (1984)

Background. The Lynn Pierson Therapeutic Research Program continued in 1984 (Behavioral Science Division 1984).

Treatment Method. The program was similar to that in 1983, with the exception that some patients received only one treatment and others received an average of six treatments after chemotherapy. Patients were randomly assigned to the same treatment groups as in the 1983 protocol. The protocol also allowed patients options to begin in one treatment group and switch to another, to refuse to be in the smoking group, or to try both routes of administration sequentially. Success was defined as a reduction in nausea and vomiting, and failure was defined as no reduction. Table 6 shows the results. It is important to note that few patients continued with the oral THC treatment, while those who smoked marijuana achieved over 90% success. Summarizing side effects of both THC and marijuana reported over the two years, treated patients often fell asleep. Of those who did not (approximately 90 patients), 50% reported sleepiness and 45% felt "high." No other side effects were noted in the report.

CALIFORNIA

Background. After legislation passed by the State of California Legislature in 1979, a Cannabis Therapeutic Program was carried out between 1983 and 1989 under the supervision of the California Research Advisory Panel (1989).

Treatment Method. Over the years, several protocols were used. Essentially, the early protocols were conservative, e.g., patients were required to have failed treatment with conventional anti-emetic drugs. Later, a more relaxed protocol was used in which the patient and the physician decided whether or not to try the THC capsule or smoke marijuana.

TABLE 6. New Mexico Trial (1984): Treatment Success After the First Treatment with Inhaled Marijuana or Oral THC

Group	Oral THC	Inhaled Marijuana	Combined
Success	6 (54.5%)	79 (95.2%)	79 (98.8%)
Failure	5 (45.5%)	4 (4.8%)	1 (1.2%)

Measures. Physicians used 5 point rating scales to record nausea and vomiting.

Results. Table 7 shows the combined results of the various protocols combined. In this study, smoked marijuana was consistently more effective than oral THC in blocking vomiting except in the most severe cases (> 6 times). Control of nausea was about the same for both groups. The pattern of side effects did not differ, to any extent, between smoked marijuana and oral THC.

NEW YORK

Background. The New York Department of Health study conducted a large scale (Phase III type) cooperative clinical trial (Randall, 1990).

Treatment Method. The central question addressed was how effective inhaled marijuana was in preventing nausea and vomiting due to chemotherapy in patients who failed to respond to previous anti-emetic therapy. Patients undergoing chemotherapy were allowed to use marijuana distributed through three centers: North Shore Hospital (NSH), Columbia Memorial Hospital (CMH), and a triad of the Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital (JGH). By 1985, the New York program provided marijuana therapy to 208 patients through 55 practitioners. Of those, data on 199 patients were evaluated. These patients had received a total of 6,044 NIDA-

TABLE 7. California Trials: Ratings of Nausea and Vomiting for Smoked Marijuana or the THC Capsule.

	Smoked Marijuana	THC Capsule		Smoked Marijuana	THC Capsule
Nausea			Vomiting		
None	9 (9.2%)	38 (15.1%)	None	19 (19.4%)	89 (35.3%)
Mild	34 (34.7%)	85 (33.9%)	1-3 times	36 (36.7%)	69 (27.4%)
Moderate	36 (36.7%)	73 (29.1%)	4-6 times	18 (18.4%)	35 (13.9%)
Severe	17 (17.3%)	55 (21.9%)	> 6 times	24 (24.5%)	59 (23.4%)
Missing	2 (2%)	6 (2.3%)	Missing	1 (1%)	5 (2.3%)

Side Effects (combined ratings from mild to severe are shown Table 8).

TABLE 8. California Trials: Side Effects Reported by Patients

	Smoked Marijuana n = 98	Smoked Marijuana %	THC Alone n = 257	THC Alone %
Dry Mouth	53	56.5	112	44.8
Tachycardia	6	6.4	25	10.0
Ataxia	16	27.1	31	12.8
Dizziness	31	33.1	67	26.8
Orthostatic	7	7.5	32	12.8
Anxiety	19	20.2	47	18.8
Sedation	49	52.1	160	64.0
Elated Mood	25	26.6	61	24.4
Confusion	23	26.6	79	31.6
Perceptual	15	15.9	57	22.8
Fantasizing	10	10.7	29	11.6
Depressed	17	18.1	33	13.2
Panic/Fear	7	7.5	9	7.6

supplied marijuana cigarettes provided to patients during 514 treatment episodes.

Measures. Observations were made by patient self-report.

Results. North Shore Hospital reported marijuana was effective at reducing emesis 92.9% of the time; Columbia Memorial Hospital reported efficacy of 89.7%; the triad of Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital reported 100% of the patients smoking marijuana gained significant benefit.

Analyzing patient evaluations, the report concluded that approximately 93% of marijuana inhalation treatment episodes were effective or highly effective when compared with other anti-emetics. The New York study reported no serious adverse side effects. No patient receiving marijuana required hospitalization or any other form of medical intervention.

DISCUSSION

Even though slightly different methods and different research designs were used in these studies, it is clear that inhaled marijuana was

effective in reducing or eliminating nausea and vomiting following cancer chemotherapy. In those studies which compared the inhalation route to oral THC, inhalation was equal to or better than oral administration. In almost all of these studies, patients were admitted only after they failed treatment with standard anti-emetics, suggesting the patients may have been under fairly aggressive treatment for their cancers.

With regard to side effects, short term use of marijuana leads to sedation, a high, and smoke intolerance in some patients. At this point in time there is no conclusive evidence that marijuana smoke seriously affects the immune system or is associated with cancer (Joy, Watson and Benson, 1999).

In a 1991 survey, Doblin and Kleiman (1991) reported that more than 70% responding oncologists (n = 1035) reported at least one of their patients had used marijuana as an anti-emetic, and that they had also either observed or discussed the patients' use. In addition, 44% of the respondents reported recommending marijuana to at least one patient. Two hundred seventy-seven respondents felt they had clinical experience with both marijuana and Marinol™ (oral THC): (44% thought marijuana was more effective, 43% thought they were about equally effective, and 13% thought Marinol™ was more effective). These data suggest that physicians at that time continued to discuss or recommend marijuana use to some patients. In this sample of oncologists, it seems they understood the potential efficacy of marijuana use. Whether this situation has changed since 1991 is unknown, but one might argue that the introduction of the anti-emetics of the selective serotonin-3 antagonist class, may have changed this practice.

While there have been no studies which have compared smoked marijuana or Marinol™ with the serotonin receptor type-3 antagonists (granisetron or ondansetron), it is instructive to review published clinical trials with these compounds for the sake of comparison. In 9 clinical trials with ondansetron, anti-emesis was obtained in 40%-81% (mean 63.5%) of patients (Beck et al. 1993; Buser et al. 1993; Crucitt et al. 1994; Hainsworth et al. 1991; Herrstedt et al. 1993; Kaasa et al. 1990; Marty et al. 1980; Olver et al. 1996; Roila et al. 1991). In 5 clinical trials with granisetron, 37.7%-93% (mean 56.6%) anti-emesis was reported (Italian Group for Antiemetic Research 1995; Markman et al. 1996; Perez et al. 1997; Ritter Jr. et al. 1998; Sekine et al. 1996). It is generally known that combining anti-emetic drugs with different

mechanisms of action often improves efficacy (Jones et al. 1991). This suggests that future research should consider combining cannabinoids with other anti-emetics.

The data reviewed here suggest that the inhalation of THC appears to be more effective than the oral route. In order to achieve the IOM recommendation to allow patients access to marijuana, both state and Federal Governments would need to reschedule marijuana from Schedule I to Schedule II, or reinstate the Compassionate Use Program. The development of smokeless inhalation devices would certainly be an advance in the use of THC as an anti-emetic medication. Finally, a large number of synthetic cannabinoid and endocannabinoid agonist analogs have been developed. It would seem that testing of these compounds as potential anti-emetics would also be worthwhile.

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The Endocannabinoid System: Can It Contribute to Cannabis Therapeutics?

Vincenzo Di Marzo

ABSTRACT. Receptors for Δ^9-tetrahydrocannabinol (THC), cannabis' major psychoactive principle, have been identified in animal tissues. These proteins have a reason to exist because endogenous substances may bind to and functionally activate them, thereby producing pharmacological effects similar to those of THC. Such substances, named "endocannabinoids," have been isolated and several studies have been performed on their pharmacological properties as well as on the molecular mechanisms for their biosynthesis, action and inactivation in animal cells. Within the framework of the ongoing debate on the therapeutic potential of cannabinoid receptor agonists and antagonists, the present article addresses the possibility that our knowledge of the endocannabinoid system may result in the development of new drugs for the treatment of illnesses as diverse as nervous and immune disorders, pain, inflammation and cancer.

KEYWORDS. Cannabinoids, endocannabinoids, endogenous cannabinoids, anandamide, 2-arachidonoyl glycerol, receptors

THE ENDOCANNABINOID SYSTEM

Research on the mechanism of action of the psychoactive components of *Cannabis sativa*, the cannabinoids, culminated in the early

Vincenzo Di Marzo, PhD, is affiliated with the Istituto per la Chimica di Molecole di Interesse Biologico, Consiglio Nazionale delle Ricerche, Via Toiano 6, 80072, Arco Felice, Napoli, Italy (E-mail: vdimarzo@icmib.na.cnr.it).

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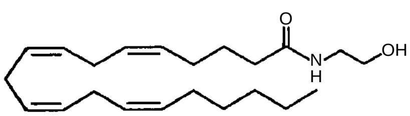
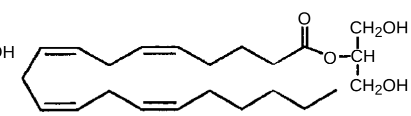
1990's with the finding of cannabinoid receptors and of their possible endogenous agonists (see Matsuda 1997 and Di Marzo 1998 for reviews) (Figure 1). These molecules, together with the proteins that regulate their activity and/or levels, constitute the ''endocannabinoid system.'' The first subtype of cannabinoid receptors, named CB_1, is widely distributed in both nervous and non-nervous tissues, and is responsible for most of the 'central' actions, and also for some of the peripheral ones, of plant and synthetic cannabinoids. The second subtype of cannabinoid receptors, named CB_2, has been found to date in high levels only in immune tissues and cells and may mediate some of the immune-modulatory effects of the cannabinoids, although little direct evidence for this possibility has been found so far. Evidence for CB_2-like receptors in peripheral nerves has been also described (Griffin et al. 1997). The finding of selective CB_1 and, more recently, CB_2 receptor antagonists (Rinaldi-Carmona et al. 1994, 1998; Felder et al. 1998), and the development of cannabinoid receptor knockout mice (Ledent et al. 1999; Zimmer et al. 1999; Buckley et al., 1999) will

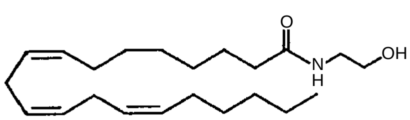
FIGURE 1. Chemical structures and likely molecular targets of the endocannabinoids and other cannabimimetic fatty acid derivatives.



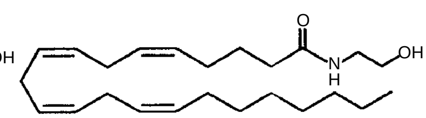
Anandamide (CB_1)



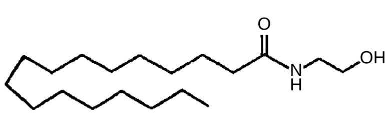
2-Arachidonoyl glycerol (CB_1 and CB_2)



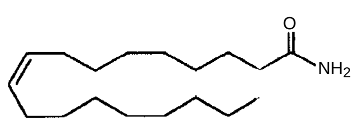
Di-homo-γ-linolenoylethanolamide (CB_1)



Docosatetraenoylethanolamide (CB_1)



Palmitoylethanolamide (?)



Oleamide (FAAH, 5-HT receptor)

soon provide a definitive answer as to which of the typical pharmacological actions of cannabinoids are mediated by either receptor subtype, and may even support the hypothetical presence of further molecular targets for these compounds. As to the possible endogenous counterparts of the cannabinoids, over the last seven years several fatty acid derivatives have been found to mimic the properties of Δ^9-tetrahydrocannabinol (THC), cannabis' major psychoactive principle. Not all of these substances, however, have the capability to displace high affinity cannabinoid ligands from selective binding sites in membrane preparations containing the CB_1 or the CB_2 receptor. Anandamide (Devane et al. 1992), the amide of arachidonic acid with ethanolamine, was the first of such compounds to be isolated and received its name from the Sanskrit word for ''internal bliss,'' *ananda*. Next came two polyunsaturated congeners of anandamide (Hanus et al. 1993), and a glycerol ester, 2-arachidonoyl glycerol (2-AG) (Mechoulam et al. 1995; Sugiura et al. 1995). These compounds share the ability to bind to and activate CB_1 and (particularly in the case of 2-AG) CB_2 receptors. Therefore, they induce a series of pharmacological effects *in vitro* and *in vivo* that are, to some extent, similar to those exerted by THC (Hillard and Campbell 1997; Di Marzo 1998; Mechoulam et al. 1998). Hence the name of ''endocannabinoids'' was proposed for anandamide and 2-AG. Other fatty acid derivatives (Figure 1), such as palmitoylethanolamide and *cis*-9-octadecenoamide (oleamide), do not have high affinity for either of the two cannabinoid receptor subtypes discovered so far, and yet they exhibit pharmacological actions that in some cases are cannabis-like (see Lambert and Di Marzo 1999 for review). The molecular mode of action of these latter compounds, that cannot be referred to as ''endocannabinoids,'' is currently being debated and is possibly due in part to the modulation of either the action or the metabolism of anandamide and 2-AG (Mechoulam et al. 1997; Lambert and Di Marzo 1999).

The study of the pharmacological properties of the endocannabinoids was not limited to confirm for these compounds the same spectrum of activities previously described for THC. Indeed, qualitative and quantitative differences between the action of classical and endogenous cannabinoids became evident since the first studies on these new metabolites (Hillard and Campbell 1997; Di Marzo 1998; Mechoulam et al. 1998). The chemical structure of anandamide and 2-AG (Figure 1), with the presence of hydrolysable amide or ester bonds and

of an arachidonate moiety, raises the possibility that these substances may be metabolized to other bioactive compounds through the several oxidizing enzymes of the arachidonate cascade (Burstein et al. 2000). Moreover, the lack of chiral centers contributes to making these molecules capable, in principle, of interaction with many molecular targets. The endocannabinoids, therefore, are ideal templates for the development of new drugs. Three different pieces of information are necessary in order to understand whether an endogenous substance can represent the starting point for the design of therapeutic agents. First, its pharmacologically activity *in vitro* and *in vivo* needs to be thoroughly assessed. Next, the biochemical bases for the biosynthesis, action and degradation of the substance need to be fully understood. Finally, a correlation between the occurrence of particular physiological and pathological conditions and the levels of this metabolite in tissues must be investigated. In this article, I will briefly describe the landmarks in these three aspects of the research on endocannabinoids. I will also provide a few examples of how endocannabinoid-derived molecules might turn out to be useful in the alleviation and cure not only of those illnesses traditionally treated with cannabis preparations, such as inflammation, nausea, diarrhea, and chronic pain, but also for cancer, mental disorders and immune diseases.

ENDOCANNABINOID PHARMACOLOGY: MORE THAN MEETS THE EYE

As mentioned above, anandamide, in some cases, exhibits effects qualitatively and quantitatively different from those of the classical cannabinoids. This may be partly due to the rapid metabolism of this compound both *in vitro* and *in vivo* (Deutsch and Chin 1993; Willoughby et al. 1997), but also to the fact that anandamide is a partial agonist in some functional assays of CB_1 and CB_2 activity (Mackie et al. 1993; Breivogel et al. 1998). Moreover, recent studies seem to suggest that this compound is able to adapt to binding sites within other receptors (Hampson et al. 1998; Kimura et al. 1998; Zygmunt et al. 1999). The selective antagonists developed so far for cannabinoid receptors (Rinaldi-Carmona et al. 1994, 1998) have been and still are useful tools to understand when and where anandamide effects are mediated by these proteins. It is still difficult at this stage to distinguish, among these effects, those with a physiological or therapeutic

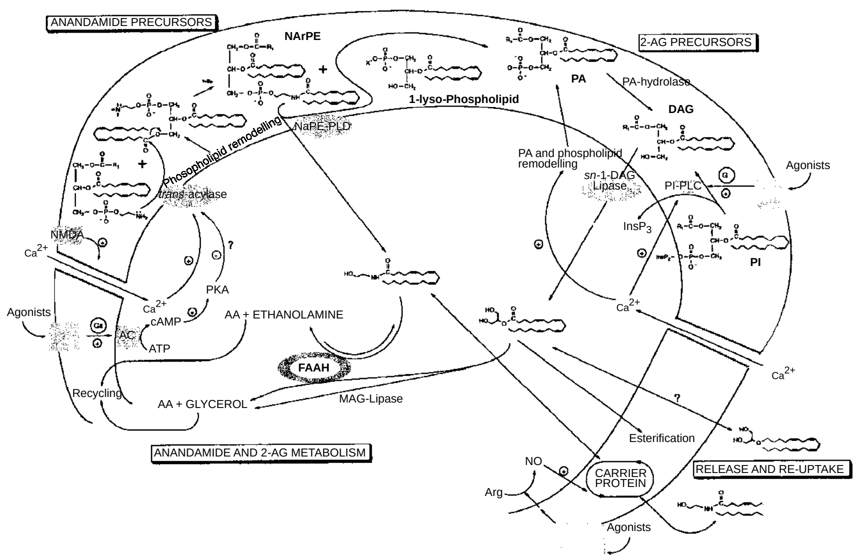
relevance. However, it is possible to speculate based on the range of concentrations necessary to observe a certain effect as compared to the usually low tissue concentrations of anandamide. Thus, in the brain, this metabolite was shown to exert inhibitory actions on learning and memory (Mallet and Beninger 1996; Castellano et al. 1997), to modulate the extra-pyramidal control of motor behavior (Romero et al. 1995), and to protect astrocytes against inflammatory stress (Molina-Holgado et al. 1997). These effects are probably due to the capability of anandamide to induce, via activation of CB_1 receptors, a series of intracellular events resulting in the modulation of neurotransmitter release, action and re-uptake (see Di Marzo et al. 1998b for review). This neuromodulatory action may also underlie anandamide regulation of hormone release at the level of the hypothalamus/pituitary/adrenal axis (Fernandez-Ruiz et al. 1997), as well as the anti-nociceptive effects of the compound through both spinal and supra-spinal mechanisms (reviewed by Martin and Lichtman 1998). In peripheral tissues, anandamide regulates the heartbeat and vascular blood pressure and produces vasodilator effects through several possible mechanisms (recently reviewed by Kunos et al. 2000). The endocannabinoid also relaxes smooth muscle in the gastrointestinal system and reproductive/urinary tract (Pertwee and Fernando 1996; Izzo et al. 1999). Regulation of reproduction also occurs at the level of the sperm acrosome reaction (Schuel et al. 1994) and embryo development and implantation (Paria et al. 1995, 1998). As most of these findings were obtained after the development of the CB_1 receptor antagonist SR141716A (Rinaldi-Carmona et al. 1994), it was possible to demonstrate the intermediacy of this receptor in most of the above effects. Conversely, the involvement of CB_2 receptors in the immune-regulatory effects of anandamide is yet to be fully established (for a recent review see Parolaro 1999), probably due to the only very recent availability of a selective antagonist for these receptors, SR144528 (Rinaldi-Carmona et al. 1998). Finally, anandamide was also found to regulate some key cell functions such as cell proliferation and energy metabolism (De Petrocellis et al. 1998, Guzman and Sanchez 1999), but only in the first case by activating CB_1 receptors. As to 2-AG, only a few pharmacological studies have been performed to date on this compound, possibly because of its limited commercial availability until recently. Apart from its activity in the mouse ‘‘tetrad’’ of tests for cannabimimetic compounds (i.e., analgesia in the ‘‘hot-plate’’ or ‘‘tail-

flick'' test, immobility on a ring, hypothermia and inhibition of spontaneous activity in an open field [Mechoulam et al. 1995]), this compound shares with THC an immune-modulatory action (Ouyang et al. 1998) and an inhibitory effect on embryo development (Paria et al. 1998) and breast and prostate cancer cell proliferation (De Petrocellis et al. 1998; Melck et al. 2000). 2-AG also induces calcium transients in neuroblastoma × glioma cells and HL-60 cells (via CB_1 and CB_2 receptors, respectively), an effect that is not efficaciously exerted by anandamide (Sugiura et al. 1999, 2000). Therefore, different pharmacological actions can be observed not only for *endo*cannabinoids and *exo*cannabinoids, but also for anandamide and 2-AG.

LEVELS OF ENDOCANNABINOIDS IN TISSUES: PHYSIOLOGY AND PATHOLOGY

Biochemical pathways for anandamide and 2-AG biosynthesis and inactivation by intact cells have been identified (see [Hillard and Campbell 1997; Di Marzo 1998; Di Marzo et al. 1998] for reviews) (Figure 2). Mechanisms for the regulation by both physiological and pathological stimuli of the enzymes involved in these pathways have also been found. On stimulation with calcium ionophores, or other calcium mobilizing stimuli, anandamide is produced by neurons and leukocytes from the hydrolysis of a membrane phospholipid precursor, *N*-arachidonoyl phosphatidyl ethanolamine (NArPE). The reaction is catalyzed by a phospholipase D specific for NArPE and other homologous phospholipids. Notably, phospholipase D enzymes are known to be subject to regulation by intracellular mediators (e.g., the diacylglycerols). NArPE, in turn, is produced by the transfer of arachidonic acid from the *sn*-1 position of phospholipids onto phosphatidylethanolamine. The enzyme involved in this case is a *trans*-acylase regulated by calcium and cAMP-induced protein phosphorylation. 2-AG is produced in intact neurons from the hydrolysis of diacylglycerols catalyzed by the *sn*-1 selective diacylglycerol lipase. Diacylglycerols serving as 2-AG precursors are in turn formed from the hydrolysis of either phosphatidylinositol or phosphatidic acid. The enzymes catalyzing these two reactions are a phospholipase C and a phosphatidic acid hydrolase, respectively. There is no evidence that these two enzymes are different from enzymes of the same type responsible for

FIGURE 2. Schematic representation of endocannabinoid biosynthetic and metabolic pathways describes so far in intact cells. Adapted from Di Marzo et al., 1998b. Abbreviations: NMDA, N-Methyl-D-Aspartate; NaPE-PLD, N-acyl-phosphatidylethanolamine-selective phospholipase D; PI-PLC, phosphatidylinositol-selective phospholipase C; PA, phospatidic acid; DAG, diacylglycerol; AC, adenylyl cyclase; PKA, protein kinase A; MAG, mono-acylglycerol; NO, nitric oxide; AA, arachidonic acid; FAAH, fatty acid amide hydrolase.



the formation of intracellular mediators, and therefore it is likely that they are subject to several regulative mechanisms.

Also the routes leading to endocannabinoid degradation are likely to be tightly regulated (Hillard and Campbell 1997; Di Marzo 1998; Di Marzo et al. 1998b). The major enzyme responsible for anandamide hydrolysis, fatty acid amide hydrolase (FAAH), has been cloned from four species (Cravatt et al. 1996; Giang and Cravatt 1997; Goparaju et al. 1999) and found to contain a proline-rich domain necessary for enzymatic activity (Arreaza and Deutsch, 1999). This domain contains a consensus sequence for recognition by regulatory proteins that may target FAAH to its subcellular location, thereby regulating its activity. FAAH also recognizes as a substrate 2-AG (Goparaju et al. 1998), for which, however, other hydrolytic enzymes have been described. One of these hydrolases, present in rat platelets and macro-

phages, is down-regulated by lipopolysaccharides (LPS) exposed by bacterial walls (Di Marzo et al. 1999).

As the hydrolytic enzymes responsible for the degradation of endocannabinoids seem to be located in intracellular sites (Giang and Cravatt 1997), the internalization of these compounds is necessary for their degradation to occur. A mechanism for the facilitated diffusion of anandamide across the cell membrane has been identified in several cell types. This "carrier" is temperature-dependent, saturable, quite selective for anandamide and some of its analogues, and sensitive to specific inhibitors (Beltramo et al. 1997; Hillard et al. 1997; Di Marzo et al. 1998a; Melck et al. 1999). More importantly, the anandamide carrier is activated by nitric oxide (Maccarrone et al. 1998, 2000), a finding that creates the possibility of regulatory loops between the action of some mediators or pathological stimuli and anandamide inactivation.

The observations described above suggest that the levels of pharmacologically active endocannabinoids in tissues may change during a certain physiological or pathological response and, therefore, that substances interfering with anandamide or 2-AG biosynthesis, action and metabolism may be used as therapeutic agents. However, over the last six years, only a few studies have attempted to correlate endocannabinoid levels with particular physiopathological conditions. Pioneering studies have been carried out in peripheral tissues. Anandamide was produced in the highest levels in the mouse uterus when this tissue is least receptive to the embryo (Schmid et al. 1997). This finding and the observation that anandamide inhibits embryo implantation (Paria et al. 1995, 1998) suggest that a defective regulation of endocannabinoid levels in the uterus may underlie early pregnancy failures. If this is proven to be the case, inhibitors of anandamide synthesis, or CB_1 receptor antagonists, could be used to prevent this clinical problem. Formation of 2-AG in platelets and of both 2-AG and anandamide in macrophages was correlated with septic shock-induced hypotension in rats (Varga et al. 1998). In fact, macrophages and platelets from rats treated with LPS were shown to induce CB_1-mediated hypotension in untreated rats. Likewise, macrophages from rats undergoing hemorrhagic shock produce anandamide and induce hypotension in untreated rats in a fashion sensitive to the CB_1 antagonist SR141716A (Wagner et al. 1997). In this case, THC treatment was found to improve the chances of survival of rats after hemorrhagic shock, whereas

SR141716A appeared to rescue the animals from septic shock. These data underlie the importance of studies on the endogenous cannabinoid system for the development of alternative therapeutic approaches.

In the brain, anandamide, but not 2-AG, was found to be released from the dorsal striatum of freely moving rats and shown to counteract the motor-inducing action of the dopamine D2 receptor agonist quinpirole (Giuffrida et al. 1999). This finding is in agreement with data suggesting for anandamide a role in the extra-pyramidal control of locomotion, possibly at the level of dopamine action (Romero et al. 1995). A more recent study showed that endocannabinoid levels in the external layer of the globus pallidus are inversely correlated with spontaneous motor activity in the reserpine-treated rat, an animal model of Parkinson's disease (Di Marzo et al. 2000a). Out of the six brain regions analyzed, only the globus pallidus–an area which receives CB_1–containing GABAergic terminals from the striatum, and where both classical and endogenous cannabinoids potentiate GABA inhibitory action on movement (Wickens and Pertwee 1993)–was found to contain *increased* amounts of 2-AG concomitantly to the akinesia induced by reserpine-mediated catecholamine depletion in the striatum. Both anandamide and 2-AG levels in the globus pallidus were *reduced* concomitantly to the administration to reserpine-treated rats of dopamine receptor agonists and the subsequent partial recovery of motor behavior. Finally, co-administration to rats of quinpirole and the CB_1-antagonist SR141716A almost totally restored normal locomotion. On the other hand, it was also found that the dyskinesia induced in MTPT-treated monkeys after prolonged treatment with L-dopa, a typical consequence of curing Parkinson's disease in humans with this drug, was alleviated by SR141716A (Fox et al. 1999). These studies suggest that agonists and antagonists of CB_1 receptors may be used advantageously in the future for the treatment of parkinsonian patients. Furthermore, these data reveal the existence of a complex regulatory interplay between the dopaminergic and endocannabinoid systems, according to which activation of dopamine receptors may either activate or inhibit endocannabinoid signaling, and endocannabinoids would either counteract or reinforce dopamine action, depending on the brain region and the pathophysiological situation. Indeed, this interplay may occur also at the level of the limbic system and underlie a role of endocannabinoids in the reinforcement of, or the recovery from, the effects of prolonged drug abuse. In fact, a recent

study showed that chronic treatment of rats with THC results in the down-regulation of cannabinoid receptor binding and signaling in all brain regions analyzed except for the limbic forebrain, where these two parameters were not altered (Di Marzo et al. 2000c). This region was also the only one exhibiting higher amounts of anandamide with respect to vehicle-treated rats. It is possible that dopamine released in the nucleus accumbens following chronic administration with THC (or more potent drugs of abuse, such as morphine and alcohol) (Tanda et al. 1997) stimulates the formation of anandamide in this region, by analogy to what was previously found for the dorsal striatum (Giuffrida et al. 1999). In any event, this finding may suggest the involvement of the endocannabinoid system in motivation and reward, thus opening the way also to the possibility that drugs derived from anandamide and 2-AG be used in the treatment of depression, and related nervous disturbances.

The finding of anandamide and 2-AG in the hypothalamus of rats (Gonzales et al. 1999) and of CB_1 receptors in some nuclei such as the arcuate nucleus and the medial preoptic area (Fernandez-Ruiz et al. 1997) supports the notion, based on the well known appetite-stimulating, anti-emetic and hypothermic properties of THC, that the endocannabinoid system may be involved in the control of hypothalamic functions. Further studies are now required to understand whether endocannabinoid levels can be associated with hyperphagia or anorexia, and be tuned by the several transmitter systems that intervene in the regulation of food intake.

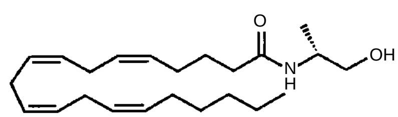
Finally, a possible correlation between anandamide release from neurons of the periaqueductal grey (PAG), a region of the brainstem, and anti-nociception was recently described (Walker et al. 1999). Electrical stimulation of the PAG results in CB_1-mediated analgesia and the release of anandamide in micro-dialysates from this region. Small amounts of the endocannabinoid were released from the PAG also following a nociceptive stimulus such as the injection of formalin into the hindpaw (Walker et al. 1999). The same stimulus does not lead to the local formation of anandamide, 2-AG or palmitoylethanolamide in the hindpaw (Beaulieu et al. 2000). Therefore, it is possible that anti-nociceptive endocannabinoids are formed at a supraspinal level following noxious stimuli. However, it is not clear how the low concentration of anandamide found in PAG microdialysates (~180 pM) can be consistent with the weak analgesic effect observed with this

compound following intrathecal, systemic and, particularly, intra-cerebroventricular administration (Calignano et al., 1998; Martin and Lichtman 1998), or with the high nM concentrations required for this compound to activate CB_1 receptors (Hillard and Campbell 1997).

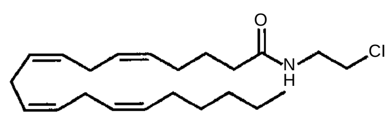
NEW DRUGS FROM THE ENDOCANNABINOID SYSTEM. CURATIVE OR PALLIATIVE?

From the findings described in the previous sections, it is clear that the discovery of endocannabinoids opens several unprecedented possibilities for the development of new drugs. Firstly, the finding that a novel class of compounds derived from fatty acids and different from classical cannabinoids and aminoalkyl-indoles could activate the cannabinoid receptors stimulated the synthesis of several new endocannabinoid-based compounds (see Martin et al. 1999, for a comprehensive review). Some of these compounds (Figure 3) are several-fold more potent than anandamide and 2-AG at CB_1 receptors, while others are

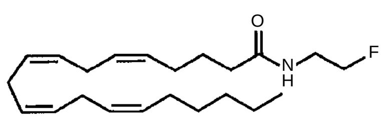
FIGURE 3. Chemical structures of potent synthetic anandamide analogues with high affinity for CB_1 receptors and/or enhanced metabolic stability.



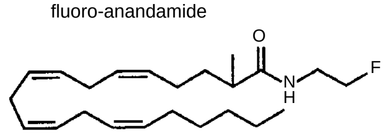
(*R*)-methanandamide



chloro-anandamide



fluoro-anandamide



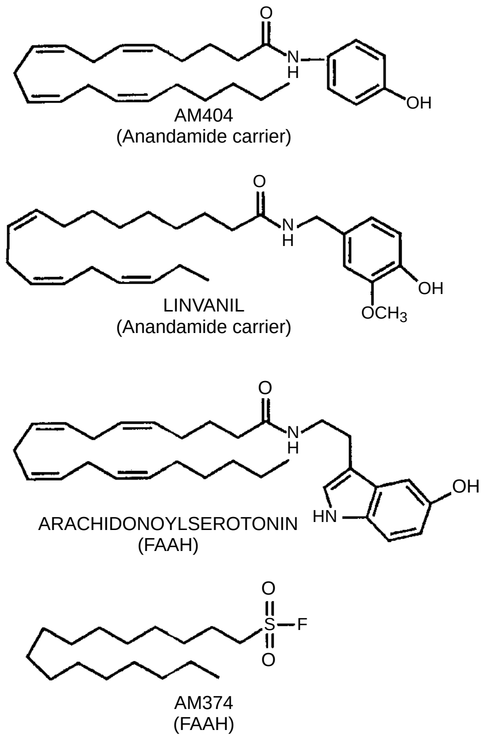
α-methyl-fluoro-anandamide

more resistant to enzymatic hydrolysis and can exert longer-lasting pharmacological actions. Secondly, when a cause and effect relationship is established between certain pathological conditions and the levels of endocannabinoids (measured by sensitive analytical techniques as in some of the studies described in the previous section), the application of endocannabinoid-based drugs for the cure of these disorders will be possible. In fact, these studies should provide indispensable hints as to what pathological state can be treated with CB_1 and CB_2 agonists or antagonists. Thirdly, our knowledge of the enzymes regulating endocannabinoid levels will allow us to develop selective inhibitors to be used for those disorders for which a correlation with defective endocannabinoid synthesis or inactivation is clearly demonstrated. Indeed, a few such substances are already available, as in the case of the rather selective inhibitors of FAAH and the anandamide carrier shown in Figure 4. Some of these compounds, such as AM404 and linvanil (two carrier inhibitors) and AM374 (a FAAH inhibitor) have been shown to lower the concentration threshold for anandamide activity both *in vivo* and *in vitro* (Beltramo et al. 1997; Gifford et al. 1999; Maccarrone et al. 2000). These compounds may be useful for those yet-to-be discovered pathological states arising from excessive degradation of endogenous anandamide. Moreover, if ways to target them selectively to peripheral tissues are devised, these compounds may render locally active doses of exogenous anandamide analogues that are devoid of undesired psychotropic activity.

Indeed, the development of new therapeutic agents from the endocannabinoids may provide a way out of the social and legal implications arising from the prescription of medical cannabis, at the center of heated debates in the UK and USA. In fact, given the numerous differences found so far between the pharmacological effects of the endogenous compounds and THC, it is likely that endocannabinoid-like drugs may have beneficial effects by simply compensating for possible malfunctions in the endogenous system, without causing the ''high'' typical of marijuana intoxication. Indeed, a recent study showed that both anandamide and its metabolically stable analogue (*R*)-methanandamide (Figure 3) do not cause dependence in rats (Aceto et al. 1998).

Finally, one last issue that should be addressed in the future is whether these putative therapeutic agents will be used simply as palliatives, as the history of medicinal cannabis would suggest, or instead

FIGURE 4. Chemical structures of synthetic inhibitors of anandamide inactivation (i.e., facilitated transport into cells or fatty acid amide hydrolase-catalyzed hydrolysis).

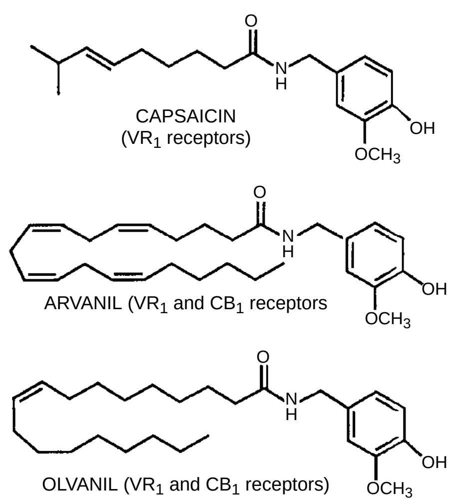


as curative drugs. The answer to this question may come from studies attempting to establish a causative role of a defective endocannabinoid system in some disorders such as, for example, those arising from exaggerated or disrupted immune responses (inflammation, allergy, auto-immune diseases), or from the hyper- or hypo-activity of the dopaminergic or other neurotransmitter systems (schizophrenia, Tourette's syndrome, anorexia, depression) (Consroe 1998). Were such a causative role to be found, metabolically stable endocannabinoids analogues and/or inhibitors of endocannabinoid degradation may contribute to the cure of these diseases. On the other hand, there may be a case for the use of exogenous endocannabinoids also in the treatment of those pathological states that are not necessarily related

to altered endocannabinoid levels and action. One example may be the recent finding of anandamide derivatives with potent anti-proliferative activity against growth factor-dependent breast and prostate cancer cell proliferation (De Petrocellis et al. 1998; Melck et al. 2000; Di Marzo et al. 2000b). One of these compounds, arvanil (Figure 5 and [Melck et al. 1999]) is a structural ''hybrid'' between anandamide and the widely used pharmacological tool capsaicin (the active principle of hot chiles), and exerts also very potent analgesic actions (Di Marzo et al. submitted). Last, but not least, the capability of endocannabinoids to synergize with opioids and opiates in the treatment of hyperalgesia and chronic pain is being debated (Manzanares et al. 1999).

In conclusion, the road to novel drugs from the endocannabinoid system is still long and unpaved. Although much progress has been done towards the understanding of the chemical bases underlying anandamide molecular recognition by cannabinoid receptors and inactivating proteins, thus leading to new pharmacologically active substances (Figures 3-5), a multi-disciplinary effort will be now required from biochemists, physiologists, pharmacologists and clinicians in order to understand whether and for what disorders these new chemicals can be used as therapeutic agents.

FIGURE 5. Chemical structures and properties of cannabinoid-vanilloid "hybrids."



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The Therapeutic Use of *Cannabis sativa* (L.) in Arabic Medicine

Indalecio Lozano

ABSTRACT. Arab scientists were several centuries ahead of our current knowledge of the curative power of hemp (*Cannabis sativa* L., Cannabaceae). Modern Western scientific literature ignores their contribution on the subject. We review in this paper the therapeutic uses of the plant in Arabic medicine from the 8th to the 18th century. Arab physicians knew and used its diuretic, anti-emetic, anti-epileptic, anti-inflammatory, painkilling and antipyretic properties, among others. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. *Cannabis sativa* L., Cannabaceae, therapeutic uses, Arabic medicine

INTRODUCTION

The modern medical and pharmacological literature which deals with the therapeutic properties of hemp (*Cannabis sativa* L., Cannabaceae) tends to ignore the valuable contributions of Arabic scientists on the subject. The tradition of the plant's medicinal use was adopted by these scientists from the cultures of the Ancient World, having been used for over a thousand years as a textile and medicine in Arabia, Mesopotamia, Persia, Egypt, China, India and extensive areas of Eu-

Indalecio Lozano, PhD, is affiliated with the Universidad de Granada, Facultad de letras, Departamento de Estudios Semíticos, 18071 Granada, Spain.

rope (Levey 1979; Escohotado 1989-1990). The role played by the medical, pharmacological and botanical literature of the Greeks in this regard is well-known, dominating medical circles in Asia Minor, Syria, Egypt and their neighbouring regions right up until the arrival of Islam in the 7th century. The *Materia medica* of Dioscorides (1st century), translated into Arabic by Istifān b. Bāsīl in the days of the caliph al-Mutawakkil (d. 861 A.D.), and the *De Simplicium medicamentorum temperamentis ac facultatibus liber VII* of Galen (d. 199 A.D.) similarly translated by Ḥunayn b. Isḥāq (d. 873 A.D.), were by far the most important sources for Arabic physicians, and were a decisive stimulus in the development of their knowledge of the plant.

To date, there are only a few works that deal with the history of the therapeutic use of hemp in Arabic medicine (Hamarneh 1972; Levey 1979; Lorano 1990), and even these only tangentially. The current renewed interest in research into the curative potential of the plant justifies a review of the subject in the light of new Arabic documental sources.

MATERIALS AND METHODS

Medical, pharmacological and botanical literature written in Arabic has been systematically and exhaustively consulted, as far as possible, from the 8th to the 18th century. Over the same period, lexicographical, agricultural, literary, legal, historical and geographical sources, which were likely to contain data on *Cannabis sativa* (L.), were also examined. The great majority were published texts, though some manuscripts were also examined. Of all the texts reviewed, more than fifty contain information on the plant, although due to limited space not all of them are mentioned in the bibliography.

In the results, we have focused our attention on the discoverer or pioneer of each therapeutic use, and only the most significant contributions of later authors have been cited. Thus, not all the sources that mention these uses have been included.

This paper arises out of a background of historical philological studies on Arabic-Islamic medicine and thus it neither can nor seeks to tackle any debate on the pharmacological mechanisms involved in the therapeutic uses documented here.

RESULTS

"Temperament" of the Plant, Parts Used, Modes of Preparation and Administration

Arab scientists explained the curative properties of hemp according to the principles of the humoral theory they learned from the Greeks. As is well-known, this theory assumes that each simple possesses a characteristic, "temperament," determined by its degrees of "heat," "cold," "wetness" and "dryness." Similarly, they largely accepted the opinion of Galen (1821-1833, VI pp. 549 f. and XII, p. 8), who talks of the desiccating and warming power of hemp. However, there is no lack of prestigious authorities who had quite the opposite opinion, stating that cannabis is naturally cold (al-Ṭabarī 1928, p. 376), or composed of hot and cold parts (al-Anṭākī, n.d., I, p. 219; al-Qūṣūnī 1979-80, I, pp. 56 f.). There is even greater controversy over the definition of the degree of heat and dryness possessed by the plant, Arab physicians citing properties from the first to the third degree. This is not surprising, if one takes into account that they could find no reference to help them in the works by Galen and Dioscorides, and that the concept of temperament and its degrees do not permit empiric proof in the sense understood by current scientific methods.

The part of the plant that was most used in therapeutic treatments was the seeds, and to a lesser extent the leaves. Methods of preparation differ according to the ailment to be treated, using the oil obtained from the seeds and the juice from the leaves and green seeds.

It was administered externally in the form of ointment in the nose, orally or in drops into the ears. Only very rarely is the actual dose which should be used in each treatment mentioned. It seems that it was commonly used as a simple medicament.

Treatment of Ear Diseases

The first mention of the curative power of hemp in Arabic literature was by Ibn Māsawayh (al-Rāzī 1968, XXI i, p. 124) (d. 857 A.D.), who refers to the oil obtained from hemp seeds and applied in drops into the ear as having the virtue of drying out the "moisture" (*ruṭūba*) generated by this organ, a curative property which later physicians attribute to the juice of these seeds. In the period in which Ibn Māsa-

wayh lived, the works of Galen and Dioscorides were translated. From them, Arabic physicians learned the use of the juice of green hemp seeds in the treatment of earache caused by an obstruction in the ear (Galen 1821-1833, VI pp. 549 ff.; Dioscorides 1957, p. 304). Continuing this tradition, in the 10th century Ishāq b. Sulaymān (1986, II, p. 133) stated that hemp seed oil relieved earache caused by the "cold" (*bard*) and the moisture in the organ, and also talked, for the first time, of its power to unblock any obstructions there. In the 13th century, the botanist from Malaga, Ibn al-Bayṭār (1291 A.H., II, pp. 115 f.) prescribed hemp seed oil to cure "gases" (*rīḥ*) in the ear. In the 14th century, Ibn al-Jaṭīb (1972, p. 69) from Granada recommended the use of this oil mixed with gum resin of *Ferula galbaniflua* to relieve "hot pain" (*al-wa¿ ḥārr*) associated with *tinnitus aurium*. In the 16th century, al-Anṭāki talks of how the leaves of "Anatolian hemp," as he calls it (*al-qinnab al-rūmī*) (Lozano 1996, pp. 152 ff.), kill the "worms" which develop in the ear, and adds that they have unblocking properties, as if you fill the ear with them, all the foreign material which is lodged there will be expelled.

Vernucide and Vermifuge

In the 9th century al-Dima¿ (Ibn al-Bayṭār 1291 A.H., IV, p. 39) is the first author who mentions the vermicidal and vermifugal properties of the plant, saying that it has the power of killing the "worms" (*al-dīdān*) that grow in the body. Between the 11th and 12th centuries, the anonymous author of the '*Umdat al-ṭabīb* (1990, Il, n° 2149) asserted that anyone who has tapeworms should eat hemp seeds, as their shells fill up with the parasites and are then expelled with them in the feces. Between the 14th and 15th centuries al-Firūzābādī (1952, I, p. 203) states that if the seeds of the plant are ingested or applied in the form of ointment over the stomach, this kills ascaris (*ḥabb al-qar'*).

Treatment of Skin Diseases

Ibn Māsawayh (al-Rāzī 1968, XXI i, p. 124) is the first author who refers to the use of hemp in the treatment of pityriasis (*ibriya*) and lichen (*ḥazāz*), and suggests that the affected part of the body should be washed with the juice from the leaves. In the 11th century Avicenna

(1294 A.H., I, p. 434) recommends oil from the seeds for the same purpose. Al-Fīrūzābādī (1952, I, p. 203) asserts that hemp seeds can be used to treat vitiligo (*al-bahaq*) and leprosy (*al-baraṣ*).

With regard to the treatment of skin diseases, and halfway between dermatology and cosmetics, al-Rāzī (al-Bīrūnī 1973, I, p. 33) (d. 925 A.D.) was the first to prescribe the use of hemp leaves as a substitute for *Melia azedarach* (L.) (Meliaceae) to stimulate hair growth. According to Ibn [illegible] 100 A.D.) the leaves should be macerated in water and then applied to the roots of the hair.

Purging Qualities

The first reference to the purging properties of hemp is made by al-Dima[illegible] (Ibn al-Bayṭār 1291 A.H., IV, p. 39), who states that the juice from hemp seeds, administered through the nose, purges the brain. In the 9th century this use is also cited by Ṯābit b. Qurra (1928, p. 21, 97), who includes hemp among the simples that can purge the upper part of the liver and eliminate any obstruction produced in this organ. He prescribes that the hemp seeds should be taken with honey mixed with vinegar.

Diuretic Properties

The pioneer of the diuretic power of hemp seeds is Isḥāq b. ʻImrān (Ibn al-Bayṭār 1291 A.H., IV, p. 39) (d. 907 A.D.). In the opinion of Isḥāq b. Sulaymān (1986, II, p. 133), this property is due to their warming power.

Antiepileptic Properties

Between the 10th and 11th centuries al-Ma[illegible]sī (1877, II, p. 116) talks for the first time of the use of hemp in the treatment of epilepsy and prescribes that the patient should be given the juice of the leaves through the nose. In the 15th century, al-Badrī (Lozano 1989-90, p. 174 f.) provides us with a spurious tale in which hemp leaves are presented as a remedy that gives an immediate cure to epilepsy.

Carminative Properties

The carminative properties of hemp seeds, already known by Galen, are mentioned for the first time by Isḥāq b. Sulaymān. Al-Ma¿sī (1877, II, p. 116) writes that the leaves have the same property and adds that they can be used to treat gases generated in the uterus, intestines and stomach.

Treatment of Abscesses and Tumours

Between the 11th and 12th centuries Ibn Buklāri¿ ° 679) prescribes the juice from hemp leaves to cure abscesses (*jurā¿t*) occurring in the head. One century later, Ibn al-Bayṭār states that if an "oily wax" made with hemp seed oil is applied to hardened tumours (*al-awrām al-¿siya*), they dissolve.

Liquification and Purging of Humors

Isḥāq b. Sulaymān mentions for the first time that hemp seeds increase the liquidity of the corporal humors. Al-Ma¿ūsī (1877, II p. 116) attributes the same property to the leaves of the plant and says that they can be used to purge phlegmatic excretions from the stomach. Ibn Habal (1362 A.H. II, p. 185) (d. 1213 A.D.) indicates that hemp seeds are good for evacuating bile and phlegm.

Treatment of the Hardening and Contraction of the Uterus

Ibn al-Bayṭār (1291 A.H., II, p. 116) prescribes hemp seed oil for treating these ailments.

Pain-Killing Properties

The use of hemp as a pain-killer was not limited to the treatment of earache. Ibn al-Bayṭār (1291 A.H., II, p. 116) recommends hemp seed oil for soothing neurological pains (*wa¿ sab*). Around the same time, al-Qazwīnī (1849, p. 293) (d. 1283 A.D.) says that the juice can be used to soothe ophthalmia.

Antipyretic Properties

Al-Fīrūzābādī (1952, I, p. 203) sustains that hemp seeds are an effective remedy in curing *febris quartana (hummà l-rib‘)*.

Antiparasitic Properties

Al-Anṭākī says that the boiled leaves from “Anatolian hemp” kill lice and nits if used to wash the part of the body where these parasites are.

Antiemetic Properties

The same al-Anṭākī attributes anti-emetic properties to the seeds from “Anatolian hemp.”

CONCLUSION

Arab scientists were several centuries ahead of our current knowledge of the curative power of *Cannabis sativa* (L.). They knew and used its diuretic, anti-emetic, anti-epileptic, anti-inflammatory and pain-killing virtues, among others. For this reason, it seems reasonable to suggest that the data to be found in Arabic literature could be considered as a possible basis for future research on the therapeutic potential of cannabis and hemp seeds. This would seem to be particularly necessary if we take into account that currently, the traditional use of the plant among Arab Islamic peoples of the world has almost completely disappeared due to the legal restrictions which prohibit its cultivation and use.

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Cannabis and Eicosanoids: A Review of Molecular Pharmacology

John M. McPartland

ABSTRACT. Many constituents of cannabis exhibit beneficial anti-inflammatory properties, such as ?^{9}-tetrahydrocannabinol (THC) in marijuana and gamma-linolenic acid (GLA) in hemp seed oil. The effects of these cannabis constituents on eicosanoid metabolism is reviewed. THC and GLA modulate the arachidonic acid cascade, inhibiting the production of series 2 prostaglandins and series 4 leukotrienes. Cannabinoid receptor- as well as non-receptor-mediated signal transduction pathways appear to be involved. It is proposed that THC acts as a selective cyclooxygenase-2 (COX-2) inhibitor.

KEYWORDS. Cannabis, cannabinoids, tetrahydrocannabinol, marijuana, anandamide, prostaglandins, thromboxanes, leukotrienes, phospholipase, cyclooxygenase, lipooxygenase

INTRODUCTION

Eicosanoids are bioactive compounds derived from C_{20} polyunsaturated fatty acids, and include the prostaglandins, thromboxanes, and leukotrienes. Many of these compounds originate from arachidonic

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John M. McPartland, DO, MS, is Clinical Assistant Professor, Department of Family Practice, University of Vermont College of Medicine, 53 Washington Street Extension, Middlebury, VT 05753.

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acid (AA), via a series of enzymatic transformations. Eicosanoids play roles in the regulation of immunity, inflammation, and neurotransmission (Zurier 1993).

The AA cascade is circumfused by the metabolism of endogenous cannabimimetic ligands, including anandamide (ANA) and 2-arachidonyl glycerol (2-AG). Coincidentally, the AA cascade is modulated by many exogenous cannabis compounds, such as ? ^{9}-tetrahydrocannabinol (THC) in marijuana and gamma-linolenic acid (GLA) in hemp seed oil.

Many studies concerning cannabis and eicosanoids report contradictory data. One fact seems certain: the release of AA from membrane phospholipids is stimulated by THC (Burstein and Hunter 1977) and by ANA (Wartman et al. 1995). The mechanism of this release may or may not involve cannabinoid (CB) receptors. CB receptors are proteins associated with cell membranes, consisting of single serpentine chains of amino acids, approximately 53 kiloDaltons (kDa) in size. The N-terminus of the protein is extracellular, the carboxyl terminus is intracellular, and the rest of the chain winds into seven transmembrane helices, with interconnecting loops of amino acids extending extra- and intracellularly (reviewed by Felder and Glass 1998). Two CB receptors have been identified. CB_1 receptors arise in neurons and some glial cells, primarily in the central nervous system, as well as in cells of the gut, uterus, and elsewhere. CB_2 receptors are found in immune cells (B-cells, monocytes, T-cells, etc.) and immune tissues (tonsils, spleen, etc.).

CB_1 receptors may mediate AA release, according to Hunter and Burstein (1997). These researchers attenuated THC-stimulated AA release by treating N18 mouse neuroblastoma cells with either CB_1 antisense probes or the CB_1 antagonist SR141716A. Contrarily, Felder et al. (1992,1993) reported that activated CB_1 receptors did not induce AA release. Felder and colleagues proposed that THC induced AA release by increasing intracellular calcium, a non-CB receptor effect. Increased intracellular calcium, in turn, induced AA release. Hunter and Burstein (1997) argued that Felder's transfected CHO cells may not express the signaling components required for AA release via receptors. Most recently, Pestonjamasp and Burstein (1998) decreased THC-stimulated AA release by treating murine monocyte cells with the CB_2 antagonist SR144528, suggesting the possible involvement of CB_2 receptors in THC-stimulated AA release.

Non-receptor mechanisms must be responsible for the activity promoted by cannabidiol (CBD). CBD is non-psychoactive and does not bind to CB receptors, yet it potently stimulated AA release, more so than THC (White and Tansik 1980). Similarly, cannabinol (CBN) and cannabigerol (CBG), with little receptor affinity, also stimulated AA release, at lower EC_{50} concentrations than THC (Evans et al. 1987).

AA release from membrane phospholipids is catalyzed by three enzymes, phospholipases A, C, and D. Each of these enzymes will be reviewed.

PHOSPHOLIPASE A_2

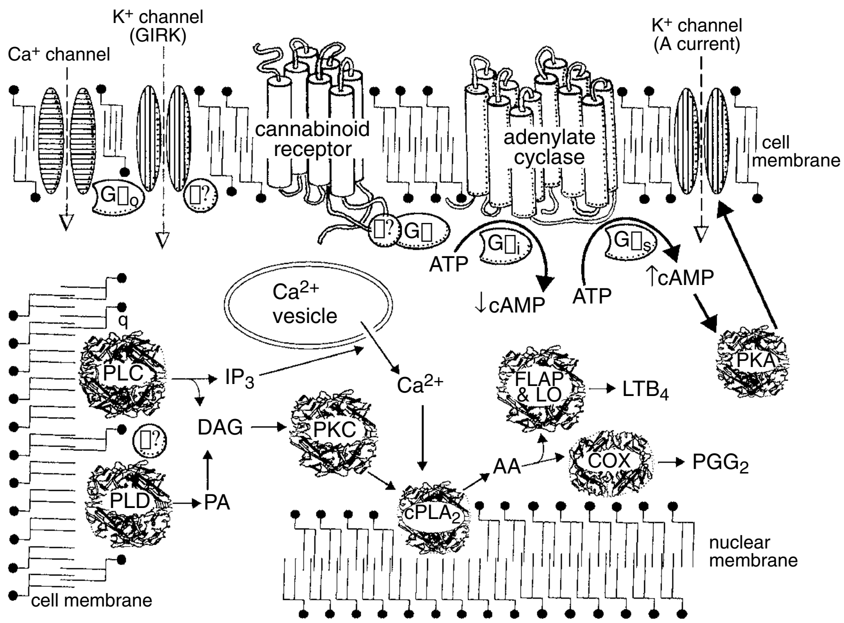
Phospholipase A_2 (P1A_2) activity increases in cells exposed to THC (Evans et al. 1987) and ANA (Wartmann et al. 1995). This enzyme hydrolyzes membrane phospholipids, particularly phosphatidylcholine and phosphatidylethanolamine, into two products–a lysophospholipid and a free fatty acid. If the fatty acid at the *sn* (stereospecific numbering)-2 position is AA, then P1A_2 releases AA in a single-step reaction. Various forms of P1A_2 have been identified. One P1A_2 specifically implicated in AA release is cytosolic P1A_2 (cP1A_2), a soluble 85 kDa protein. Upon activation, cP1A_2 translocates from the cytoplasm to the nuclear membrane, where it hydrolyzes phospholipids.

Felder et al. (1992) reported that cannabinoid-enhanced P1A_2 activity was not a receptor-mediated event. Felder et al. (1993) repeated their results using ANA. A nonreceptor mechanism must also be responsible for the potent stimulation of P1A_2 activity by CBD (White and Tansik 1980), and CBN and CBG (Evans et al. 1987).

Although currently unproven, CB receptors could indirectly enhance P1A_2 activity via G-proteins. G-proteins couple to many kinds of receptors, including those for cannabinoids, eicosanoids, opioids, epinephrine (α- and β-adrenergic receptors), acetylcholine (muscarinic but not nicotinic receptors), serotonin, dopamine, ACTH, CCK, VIP, FSH, LH, TSH, parathyroid hormone, calcitonin, somatostatin, glucagon, angiotensin II, oxytocin, vasopressin, and substance P.

G-proteins are composed of three subunits: an α subunit and a $\beta\gamma$ subunit complex (Figure 1). At least three families of G-proteins are associated with CB receptors–Gi, Go, and Gs (Glass and Felder 1997).

FIGURE 1



When a cannabinoid agonist binds to the extracellular face of a CB receptor, there is a change in the conformation of the intracellular domain of the receptor, which permits coupling of the G-protein. Coupling activates the G-protein, which quickly uncouples from the receptor and splits into its G and G? subunits. Each goes its own way, thus bifurcating the receptor signal; the signal is further amplified by the fact that each CB receptor can activate many G-proteins. Uncoupled subunits diffuse along cell membranes and influence multiple effector systems (Figure 1). G and G? subunits directly regulate ion channels, such as N-, Q-, and L-type Ca^{2+} channels, and G-protein-coupled inwardly rectifying K+ (GIRK) channels. G subunits also interact with adenylate cyclase, thus modulating the rate of cyclic AMP (cAMP) synthesis. By this mechanism, G subunits regulate the activity of cAMP-dependent protein kinase A (PKA). PKA in turn modulates the activity of transcription factors in the CREB protein family, and the transcription of genes in the nucleus.

CB receptor activation decreases cAMP production (Devane et al.

1988). Since cAMP inhibits $cP1A_2$, a CB receptor-mediated decrease in cAMP may result in a net release of AA (Di Marzo et al. 1997). Alternatively, CB receptors may act through ras and mitogen-activated protein kinase (MAPK), which phosphorylates and activates $cPlA_2$ (Wartmann et al. 1995, Di Marzo et al. 1997). Lastly, diacylglycerol (DAG), a product of other CB-receptor-mediated pathways, may activate $cP1A_2$ via protein kinase C (PKC) and MAPK.

THC actually modulates $P1A_2$ in a biphasic manner (Evans et al. 1987); low concentrations stimulate enzyme activity (EC_{50} range of 2-6 μg/ml), whereas high concentrations inhibit the enzyme (IC_{50} range of 17-48 μg/ml). To explain biphasic activity, Sulcova et al. (1998) proposed that different concentrations of ANA and THC may invoke CB receptors to couple to different G-proteins–low concentrations may activate Gs proteins (stimulatory), whereas high concentrations activate Gi proteins (inhibitory). Glass and Northup (1999) demonstrated that different agonists (THC, ANA, HU-210, and WIN 55,212-2) induced different G-protein coupling of CB receptors (Gi versus Go).

PHOSPHOLIPASE C

One type of phospholipase C (PLC) hydrolyzes a specific phospholipid, phosphatidylinositol 4,5-biphosphate, into two products that serve as second messengers: diacylglycerol (DAG) and inositol 1,4, 5-triphosphate (IP_3). DAG activates PKC, as mentioned previously, whereas IP_3 releases Ca^{2+} from intracellular stores (Figure 1). DAG can subsequently be hydrolyzed into AA and monoacylglycerol.

Felder et al. (1992) did not find CB receptors had any effect on PLC activity. This was corroborated by Glass and Northup (1999), who found CB receptors did not couple with Gαq subunits; Gαq subunits normally stimulate PLCβ activity.

PHOSPHOLIPASE D

Phospholipase D (PLD), a 100 kDa protein, hydrolyzes phospholipids into phosphatidic acid and a polar head. Phosphatidic acid is subsequently hydrolized by a phosphatase enzyme into DAG plus

phosphate. DAG can subsequently enter the DAG lipase pathway described above. Burstein et al. (1994) reported THC activated PLD, as measured by increased levels of phosphatidic acid, and they suggested the activation may be a receptor-mediated process.

AA released by phospholipase enzymes does not have a long half-life. It quickly becomes metabolized or becomes reincorporated back into phospholipids. THC, however, inhibits the reuptake of free AA into phospholipids (Reichman et al. 1991); this does not appear to be a CB-receptor-mediated phenomenon (Felder et al. 1993).

AA may be metabolized into a variety of oxygenated products via several enzymes, including (1) cycloxygenases, (2) lipoxygenases, (3) cytochrome P450 enzymes, and perhaps (4) fatty acid amide hydrolase (FAAH). Only the first two enzymes will be addressed in this review. For reviews of the latter two enzymes, see Bornheim et al. (1993) and Felder and Glass (1998), respectively.

CYCLOXYGENASE

Cycloxygenase (COX) enzymes are globular, 72 kDa proteins that associate with membrane surfaces. AA released from membranes enters a channel within COX that leads to the active catalytic site. When AA reaches the catalytic site, COX inserts two oxygen molecules and extracts a free radical from AA, resulting in the five-carbon ring that characterizes prostaglandin G_2 (PGG_2). PGG_2 is subsequently metabolized to other prostaglandins (e.g., PGE_2), prostacyclins (e.g., PGI_2), and thromboxanes (e.g., TXB_2). Note that prostaglandins derived from AA have two double bonds, indicated by the subscript 2. Prostagiandins with one or three double bonds are derived from other fatty acids (e.g., PGE_1 from dihomo-gamma-linolenic acid, and PGE_3 from eicosapentaenoic acid).

THC blocks the conversion of AA to PGE_2, presumably by inhibiting COX activity (Burstein and Raz 1972). But in subsequent studies, THC exhibited a biphasic, dose-related effect on PGE_2 release, namely, inhibition at doses of 0.016-0.16 μM and stimulation at 1.6 μM (Burstein and Hunter 1977). This biphasic activity was probably due to the release of AA by THC; i.e., increased substrate overcame COX inhibition.

Cannabinoid structures that do not activate CB_1 receptors also in-

hibit the metabolism of AA to PGE_2, including CBD, CBN, and CBC (Burstein et al. 1973). Even noncannabinoid constituents in marijuana can inhibit COX activity and PGE_2 synthesis, such as essential oils (Burstein et al. 1975), phenols (Burstein et al. 1976), and flavonoids (Evans et al. 1987). The flavonoid cannflavin A was more potent an inhibitor than THC or CBD, with an IC_{50} of 7.0 mg/ml (Evans et al. 1987). But on a weight basis, crude marijuana extracts were more inhibitory than any single constituent, suggesting that synergy occurs with individual compounds (Evans et al. 1987).

The mechanism by which cannabinoids inhibit COX remains unclear. Pro-inflammatory cytokines may be involved, such as interferon ? (INF?), interleukin-1□ (IL-1□), and tumor necrosis factor a (TNF□). COX is activated by these cytokines, and cannabinoids are known to inhibit INF? production (Klein et al. 1998a), and inhibit IL-1□ and TNF□ (Zurier et al. 1998). Inhibition of INF? by THC appears to be mediated by CB_2 receptors rather than CB_1 receptors (Klein et al. 1998a). Whereas and IL-1□ and TNF□ are inhibited by a cannabinoid without receptor affinity (Zurier et al. 1998). TNF□ is also inhibited by noncannabinoids present in cannabis, such as apigenin, a flavonoid (McPartland and Pruitt 1999).

The modulation of cytokines by cannabinoids is complex, and biphasic effects are seen (Klein et al. 1998b). Evidence suggests that cannabinoids may directly inhibit COX without involving the cytokine network.

COX ISOFORMS

Two COX isoforms exist, dubbed COX-1 and COX-2. Although they both synthesize prostaglandins, they appear to serve different functions. COX-1 is constitutively expressed, localized in the endoplasmic reticulum, and it produces prostaglandins that protect the gastric mucosa, renal parenchyma, vascular endothelium, and platelet function COX-2 is found on the nuclear envelope, it is activated during inflammatory reactions, and by proinflammatory cytokines. COX-2 activation potentiates the pain and inflammation caused by bradykinin, histamine, and leukotrienes. Lastly, COX-2 prostaglandins are manufactured by malignant cells in the colon (Sheehan et al. 1999).

The obvious goal, at least as far as pain and inflammation is concerned, is to develop drugs that block COX-2 without affecting COX-1. Standard non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, inhibit COX-2 and COX-1. Thus, NSAIDs inhibit inflammation but also predispose people to stomach ulcers and renal disease. Recently, however, "selective COX-2 inhibitors" have become available, such as celecoxib (Celebrex®) and rofecoxib (Vioxx®).

NSAIDs inhibit COX by a simple blockade of the channel that leads to the active catalytic site within COX. Selective COX-2 inhibitors exploit small differences in the shapes of COX-1 and COX-2 tunnels (Hawkey 1999). The difference between the COX isoforms is a single amino acid substitution, which produces a sidepocket in the channel of COX-2. Selective COX-2 inhibitors are bulky molecules; they fit in the COX-2 channel sidepocket, but cannot fit in the narrower channel of COX-1.

Zurier et al. (1998) studied COX inhibition by THC-11-oic acid, a metabolite of THC that is non-psychoactive and has little affinity for CB receptors. Zurier and coworkers substituted the pentyl side chain of THC-11-oic acid for a dimethylheptyl side chain. The synthetic product, termed ajulemic acid, demonstrated highly selective COX-2 activity.

It is proposed here that the bulky tricyclic ring structure of THC, like that of ajulemic acid, may provide selective COX-2 inhibition, assuming THC can gain access to cytoplasmic COX enzymes. Mechanical blockade of the COX-2 channel would not be a CB-receptor-mediated event. The hypothesis that THC and perhaps all cannabinoids selectively inhibit COX-2 is supported by the clinical observation that chronic marijuana use does not damage the gastric mucosa, unlike NSAIDs which inhibit COX-1 as well as COX-2.

Lack of gastric toxicity by cannabinoids, however, may be due to enhanced production of nitric oxide (NO). NO protects the gastric mucosa by stimulating COX-1 enzymes (Hawkey 1999), and some researchers report that cannabinoids stimulate release of NO (Stefano et al. 1996), although stimulation is not observed in all cell lines (Waksman et al. 1999).

LIPOXYGENASE

AA released by $cP1A_2$ can also be metabolized by lipoxygenase (LO) enzymes. Three types of LO enzymes, 5-LO, 12-LO, and 15-LO, are known in humans; they are associated with membranes and weigh about 75 kDa.

The 5-LO enzyme catalyzes the insertion of an oxygen molecule into AA at carbon 5, forming 5-hydroperoxy-eicosatetraenoic acid (5-HPETE), an unstable intermediate which can be further metabolized into a series of leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4). Leukotrienes cause epithelial inflammation, mucus secretion, smooth muscle contraction, and bronchoconstriction, leading to symptoms of asthma and ulcerative colitis (Drazen et al. 1999). The 15-LO enzyme converts AA into 15-HPETE, which is further metabolized to 15-hydroxy-eicosatetraenoic acid (15-HETE) or a series of lipoxins (LX_A, LX_b, etc.). These products are potential mediators of airway inflammation, and they induce hyperalgesia by increasing the sensitivity of pain fibers in the skin (Riccio et al. 1997). The 12-LO enzyme converts AA into 12-HPETE, which is subsequently reduced to 12-HETE. These products modulate neurotransmission and may have neuroprotecuve properties, as well as cardioprotective ''ischemic preconditioning'' effects, but 12-HETE also promotes tumor cell adhesion, an important factor in metastasis (Chen et al. 1997).

In a noncellular soybean LO assay, THC and CBD inhibited 15-LO activity, with IC_{50} values around 3 μM (Evans et al. 1987). Noncannabinoid constituents of cannabis, such as cannflavin, did not inhibit LO at pharmacologically relevant concentrations. Subsequently, the same research group studied the effects of THC and CBD on the 5-LO enzyme. CBD produced a 100% inhibition of LTB_4 production in human polymorphonuclear (PMN) cells, with an IC_{50} = 5.4 μM; THC was only capable of producing a 90% inhibition, with an IC_{50} = 8.2 μM (Formukong et al. 1991). This degree of inhibition is comparable to the new pharmaceutical drug zileuton (Zyflo®); a single 800 mg dose blocks LTB_4 production by 80%, although the IC_{50} = 0.5 μM (McGill and Busse 1996).

THE HEMP CONNECTION

Not all prostaglandins and leukotrienes are derived from AA. One

group of non-AA-derived eicosanoids utilizes dihomo-?-linolenic acid (DGLA) as a substrate. Prostaglandins derived directly from DGLA have one double bond, and carry the subscript 1, such as PGE_1. Another group of prostaglandins, with three double bonds, carries the subscript 3, such as PGE_3.

PGE_1 and PGE_3, unlike their PGE_2 cohorts, actually provide antiinflammatory benefits. They shift the prostaglandin cascade away from series 2 products (e.g., PGE_2), suppress monocyte production of inflammatory cytokines, suppress synovial cell hyperplasia, decrease platelet aggregation, and protect the gastric mucosa against NSAID-induced injury (reviewed by DeLuca et al. 1995).

PGE_1 synthesis can be enhanced by consuming ?-linolenic acid (GLA), the precursor to DGLA. GLA is derived from the seed oil of evening primrose (*Oenothera biennis*, with 7-9% GLA), borage (*Borago officinalis*, 17-23% GLA), black currant (*Ribes nigrum*, 15-19% GLA), and hemp (*Cannabis sativa*, 2-6% GLA).

PGE_3 synthesis is enhanced by consuming omega-3 fatty acids: eicosapentaenoic acid and docosahexaenoic acid are found in fish oils (especially cold water fish like sardines, mackerel, salmon, bluefish, herring, and, to a lesser extent, tuna); -linolenic acid (ALA) is found in the seed oil of certain plants, such as flax (*Linum usitatissimum*, containing 58% ALA), hemp (*C. sativa*, containing 15-25% ALA), and black currant (*R. nigrum*, containing 12-15% ALA).

Only hemp oil and black currant oil contain the precursors to both PGE_1 and PGE_3. Hemp oil alone has the added benefit of containing the precursors in a 3:1 ratio, the optimal ratio for human nutrition (Pate 1999).

CONCLUSIONS

This review of eicosanoids and cannabis has been limited to molecular pharmacology. Taken together, *in vitro* studies suggest that cannabinoids act as antiinflammatory agents, inhibiting the AA cascade at several levels. Antiinflammatory activity is mediated by both CB-receptor and non-receptor mechanisms.

Clinical trials concerning eicosanoids and cannabis will be surveyed in a future review. Extracts of cannabis have long been known to decrease pain and inflammation in experimental animal models and

human subjects (O'Shaugnessy 1839). Traditional healers from Eurasian cultures have used cannabis to alleviate pain and inflammation for a very long time (Mechoulam 1986). For the same purposes, cannabis tinctures were prescribed by European and North American physicians, from O'Shaugnessy's era until Anslinger's era. Modern research has documented the molecular efficacy of cannabis products. As Graham (1976) predicted, "The drug has been frowned upon, officially banned . . . but the interest of the medical profession is slowly reviving. It is not impossible that a limited but respectable niche will be established for it in therapeutics by the end of the century."

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Cognoscenti of Cannabis I: Jacques-Joseph Moreau (1804-1884)

Ethan Russo

Portrait of Moreau in 1845, by N.E. Maurin, Library of the Academy of Medicine, Paris, France.

Ethan Russo, MD, is a neurologist with Montana Neurobehavioral Specialists in Missoula. In addition, Dr. Russo is Clinical Assistant Professor, Department of Medicine, Univeristy of Washington and Adjunct Associate Professor, Univeristy of Montana.

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Jacques-Joseph Moreau (de Tours) was one of the earliest pioneers of modern psychopharmacology. Born in 1804 in Montrésor, France, Moreau pursued medical studies in Tours and Paris, subsequently studying psychiatry under the tutelage of Jean Étienne Dominique Esquirol, whose eclectic approach to healing of the mind included the prescription of therapeutic travel. As part of his duties, Moreau accompanied patients to the Orient, where he was able to observe the effects of, and partake himself of hashish, the resinous by-product of cannabis (Holmstedt 1973).

Upon his return to France, Moreau investigated the therapeutic possibilities of this substance. He likely is the character known as ''Dr. X'' who provided hashish in the form of an electuary called *dawamesk* to literary illuminati such as Théophile Gautier, Charles Baudelaire, Alexandre Dumas and Honoré de Balzac of *Le Club des Hachichins* at the *Hôtel Pimodan* in Paris.

Moreau was among the first to apply herbal pharmacology systematically to the treatment of mental illness, using the dissociative hallucinogen, *Datura stramonium* L. Solonaceae (Moreau 1841). Moreau espoused a theory that such compounds mirrored effects of insanity, and from them, physicians might gain insight into psychopathological conditions, and even their amelioration. He then applied this concept to cannabis. His 1845 book, *Du Hachisch et de l'Alientation Mentale. Études Psychologiques.* (Moreau 1845) is a classic in the field. Unfortunately, it is a document that few have actually viewed themselves. It had a limited press run, and was never reprinted until a 1980 facsimile edition was issued by Ressources of Paris and Geneva. On the infrequent occasions that original copies appear on the rare book market, prices in the thousands of dollars are obtained.

The book was not translated into English until 1973, as *Hashish and Mental Illness* (Moreau 1973), but this volume, too, is out of print. In an early passage, Moreau observes (p. 211):

> One of the effects of hashish that struck me most forcefully and which generally gets the most attention is that manic excitement always accompanied by a feeling of gaiety and joy inconceivable to those who have never experienced it. I saw in it a mean of effectively combatting the fixed ideas of depressives, disrupting the chain of their ideas, of unfocusing their attention on such and such a subject.

In his early efforts to apply this knowledge of cannabis to patients, Moreau observed mixed results, and himself questioned its utility. However, he persisted in his efforts. Subsequently, some years later, Moreau reported an in-depth case study of a man with intractable lypemania, a type of obsessive melancholia (Moreau de Tours 1857), and its apparent resolution with cannabis therapy. Spontaneous cure might be surmised, but subsequent evidence supports a rational basis for its efficacy with the work of Muller-Vahl on obsessive-compulsive disorder (Muller-Vahl et al. 1998; Muller-Vahl et al. 1999).

Close examination reveals that this article, presented here in English for the for the first time, was apparently written by one *"Homo, interne provisoire,"* but obviously under the close direction and supervision of Moreau at the *Hospice de Bicètre.* It presents an important insight into 19th century medicine, psychopharmacology and cannabis usage.

According to Bo Holmstedt (Efron 1967) (p. 7), one of Moreau's favorite pronouncements was, "Insanity is the dream of the man who is awake." Moreau died in 1884 at the age of 80.

In the intervening century, many have judged Moreau's efforts to apply cannabis therapeutically as a failure. This view is not universal, however. Professor E. Perrot of the *Faculté de Pharmacie de Paris* stated in 1926 (Rouhier 1975) (p. IX):

> The Indian hemp, to take but one example, quite cheated the hopes of Moreau de Tours, but it would be imprudent to affirm that it will not be better utilized by the psychiatry of tomorrow! [translation EBR]

This sentiment is a useful one to consider in the modern age, as the search for better pharmacotherapeutic agents continues.

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Lypemania with Stupor; Tendency to Dementia.– Treatment by the Extract (Resinous Principle) of *Cannabis indica*.– Cure. Bicètre Hospice

M. Moreau (de Tours)
(Moreau de Tours 1857)

Following the doctrine that we have heard professed numerous times by Monsieur Doctor Moreau, it is with madness as with most of the great neuroses: the type of medicine that best suits in the prodromal period or initial phase of this illness loses all or almost all its efficacy once the chronic state is declared.

At the time this medication (internal or external derivatives, baths, affusions, etc.) must be abandoned, and resumed only in the cases, happily fairly frequent, where the affliction recovers momentarily a certain acuity.

In the confirmed chronic state, the physician must have recourse, above all, if not exclusively, to the employ of medicaments capable of profoundly modifying the vitality of the organ first injured, that is to say, the brain. The opiates (useful particularly in chronic alcoholism), the extract of Indian hemp, etc., achieve this objective perfectly. The observation which follows here is an example; we have thought that this title will acutely interest our readers.

The so mentioned Louis Suzung, 18 years of age, a typesetting worker, enters the hospital for the insane (secondary section) the 5th of January 1857.

The admission document is thus composed:

Translated from French by Ethan Russo, MD.

> Ill for only one month; febrile condition, tremors; state of stupor; melancholy; refuses almost absolutely to respond. (He had had typhoid fever?)

Nevertheless, one sees, this last piece of information from the certificate is provided with some doubt; in effect, if we ask his mother, she tells us from the start that her son had had typhoid fever; but pressed to respond to the symptoms that he had presented in the course of this illness, it is no longer possible to recognize a foundation there, and furthermore, although one would admit the possibility, one could not invoke it as a point of departure for the metal affliction. For here is what his mother reported to us: ''Before having taken to his sickbed, my son was getting lost in the streets; he could not find his way, he had lost his habitual reasoning. This state lasted eight days until he was obligated to take to his bed, and he remained down for three weeks, complaining of a pain in the pit of his stomach, of an intense headache, fever, etc.; but without abdominal pains properly speaking, without diarrhea, without ringing in the ears, without epistaxis.''–He himself, when he had recovered his wits, and interrogated on this point, confirms completely that which his mother recounted, and in addition, he added to us that it was at the time of a quarrel in the attic that he became obliged to take to bed, a quarrel which serve as a point of departure of a futile motive, and due evidently to his mental state.

The father and mother of Suzung are still living, the father, being young, is graying; once married, he stood by this habit, and would drink only a few drops with a friend from time to time, but speaking of his mother, he would renew at times to the point of gaiety. He had during those times sciatic pains, and had suffered an attack of apoplexy.

The mother had suffered a typhoid fever in her youth; in 1833, an enteritis. From the age of fourteen she had been prone to neuralgic pains in the head, which in the last year had taken on an unaccustomed intensity. What is more, she had a paralyzed arm. She had from her marriage four children: two boys and two girls. One of the girls died at the age of three, during convulsions; the other was well, and presented nothing remarkable; she much resembles her father. As to the boys, who are simply the portrait of the mother, the elder became insane at the age of eighteen, at the same age accordingly as he who occupies us at this instance, and, according to the file, we see that the form of the

insanity is the same: state of stupidity, refusal to respond, lypemania, a few moments of agitation, etc. He remained in the hospital from the 11th of August to the 23rd of November, 1849. At times, he presents again with a few delirious ideas, his mother says; he becomes intoxicated, and since his departure from the hospital, he has had a sciatica.

As to Suzung, who is the subject of this observation, the day of his entry, we found him seated on his bed. His physiognomy expresses down-heartedness, anxiety; he regards everyone with fear; he complains continually; he utters a few words that he interrupts with groans, and in which there is question of *God, of offenses to Divinity, of deserved chastisements, of earthworms*, etc. He does not respond to questions to which one addresses him; he repeats a few words that he hears spoken.

The second day, a flesh wound was placed on the nape of his neck. "In good time," he says during the operation, "my God, punish me, I am well to blame." The wound modified nothing in his state. He is agitated, and also has a few moments of violence during which he seeks to strike out, and one is obliged to restrain him on the couch. There, he takes on extraordinary poses, tries to strike himself against the posts of the chair that he occupies, or the iron of the bed nearby, and if he succeeds: "There's another one killed!" he says with each blow he gives himself. Then the resumes his moaning, his incoherent words, and recites his imaginary supplications. He refuses nourishment, and it is not until after a long debate that one may make him take a bit of broth. At last, one morning, being unbound, and having evaded the surveillance of the boy, one finds him mounted on a window, and it is probable that his intention was bad.

After twenty days, the wound having produced no result, one omitted it, and the ill one was submitted to hashish, which was given to him in pills, a the dosage of 5 centigrams to start. One half-hour after the pill was taken, he was given a cup of black coffee. The administration of this medicament was continued for fifteen days, at a progressively increasing dose, and one succeeded at giving him up to 30 centigrams.

This method of treatment seemed at first to produce no change in the state of the patient. His complaints, his remarks, the form of his hallucinations did not change; he was only more dejected, he would close his eyes in a spasmodic manner; the psychic manifestations of the hashish became mingled with those of the illness, and the state of Suzung seemed considerably aggravated.

One was forced to maintain him perpetually restrained on his couch. He did not wish to accept food but from one sole service boy, who managed to make him swallow a few spoons of broth; from every other hand, he obstinately refused the food that one presented to him. He thinned down a great deal, wide eschars formed on his sacrum, on the trochanters, his elbows; but they had the aspect of sores of good nature; the general state was very grave, and inspired serious fears. He remained continually tormented by his visions, but the words by which he expressed his supplications changed: "The screw, hello! the screw, the kneading-trough, the cuts of five hundred blades, etc." Whatever the remarks he whispered, he then resumes his continual groaning. The patient was submitted to tonics.

This state perpetuated itself all the way to the month of April, the epoch in which his wounds commenced to scar. He accepted aliments more voluntarily, whoever was the person who offered them. His thinness was extreme, but in sum, his general state was less severe.

After a fortnight, the eschars were completely closed; his frailness was less marked, and because still continually prey to the same ideas, one was obliged to maintain him with the strait-jacket, but one could, on nice days, take him in the courtyard. Little by little, one saw this serious general state ameliorate; his thinness was a little less. At the same time as this physical improvement was produced, almost imperceptibly so to speak, one observed some improvements in the mental state. Thus, one was no longer obliged to retain the strait-jacket; he ate a bit on his own; but that represented all the stated progress.

More often he remained in the courtyard propped against a tree, and taking extremely grotesque poses; he made a hunchback, arranged his arms in a bizarre fashion, resting half bent on his legs, one would say that he was going to collapse on himself; he urinated in his pants, he neglected to wipe his nose, even when the nasal mucus passed his nasal orifices. In a word, he was a veritable infant of a few months for whom it was necessary to care, to dress, to clean, etc. The groans were the same, and if one spoke to him, or better, if he repeated a few of the words that he heard, or else he whispered: The screw, the trough, etc. His ideas had not changed. At diverse occasions, Monsieur Doctor Moreau compared him to these *santons* (idiots from the abuse of hashish) that the Arabs parade in Egypt. After this medicine, the primitive illness found itself almost completely effaced by the symp-

toms germane to the action of hashish. From there, it was believed possible to harbor a favorable prognosis.

This state lasted through the final days of April and almost the entire month of May. At times, one could remark that his general health was better. The thinness had disappeared, and in this physical respect, Suzung was very well. His face, so thin a few months before, was full, and likewise, this rapid passage from the state of inanition which inspired such fears.

But here in the first days of June I remarked at the evening visit that while I approached Suzung with caution, and without him seeing me, he was no longer complaining; and that as soon as I presented myself to him, the moaning commenced. Finally, one evening, the 5th of June, I was able to obtain a direct response to the question to which I addressed him. Asked about his imaginary fears, he responded to me that with respect to Monsieur Moreau he was afraid.

The following day, I was able to follow a conversation that I did not seek to prolong, and the morning of the 7th, a bit of the fear he experienced returned, it was to Monsieur Moreau that he responded. It was an immense step.

The 8th, his responses were perfectly exact to questions addressed. Asked about his past life, he gave a very good account of his profession, the attics where he had worked, of that which he had experienced during his entry to the hospital, his bed number where he resided in the infirmary, etc., etc. The memory returned for all, except for that which transpired during the time that the had been sick confined to bed in his mother's house. Nevertheless, in the midst of this return to reason, he retained a few lypemaniacal ideas, and repeated in some moments the word guillotine. As there was a concert that day, one asked if he would like to attend; he went, but complained after a few moments that the music gave him a headache, and he asked permission to retire.

The 9th, we found him in the morning occupied with reading an article that a patient had lent him, and at the evening visit, he complained of cephalalgia, perfectly explainable by the assiduousness which he had given to his reading (from 8 o'clock in the morning to 5 o'clock in the evening).–Foot bath with mustard.

The 10th, his head was yet a bit heavy, but his reason had returned completely. For him, that which had passed in these last months was nothing but a long dream of which he was very exactly aware. The guillotine, of which he had talked again a few days before, was a

ridiculous idea, he said it himself; the memory of his illness at his mother's home had returned to him. He was completely cured.

From this day, Suzung presented no remarkable phenomena, if this is not a perfect conservation of his mental faculties, and the 18th of June he was able to be returned to his family.

Homo, Provisional Intern

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Cannabis and the U.S. Controlled Substances Act

Jon Gettman

ABSTRACT. The scheduling of cannabis under the Controlled Substances Act (CSA) has established legal precedents that determine how scientific evidence affects its regulation in the United States. This background challenges three common fallacies that make it seem marijuana prohibition is the only viable policy outcome. A contemporary effort to reschedule cannabis is based on recent findings that have established that marijuana lacks the high potential for abuse required for Schedule I or Schedule II status under the CSA. The primary policy issue is not, then, whether marijuana is the best medicine but instead whether people who use it medically should be treated as criminals. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Cannabis, cannabis use, cannabinoids, marijuana, marijuana use, tetrahydrocannabinol, dronabinol, drug control, drug policy, marijuana laws

INTRODUCTION

The United States Congress established the present system of regulating drugs according to their supposed harmfulness in 1970 (US Code Cong, Adm News 1970). The Controlled Substances Act (CSA)

Jon Gettman has recently completed his PhD in public policy at George Mason University.

Address correspondence to: Jon Gettman, P.O. Box 20227, Washington, DC 20041.

created five regulatory schedules with which to classify drugs and substances (21 USC 812) according to legal and scientific criteria specified in the legislation (21 USC 812 (b); 21 USC 811 (c)). The interpretation of these statutes was subsequently clarified by the US Court of Appeals in NORML v. Ingersoll (497 F.2d 654 (1974)) and NORML v. Drug Enforcement Administration, (559 F.2d 735 (1977)). While the initial placement and scheduling of substances was set forth in the Act, Congress also provided a mechanism for making changes in the schedules. Drugs and substances can be added, rescheduled, or removed from regulation under the CSA as justified by scientific evidence and according to federal rulemaking procedures. Rescheduling proceedings require the filing of a petition by the Justice Department, the Department of Health and Human Services (DHHS), or any interested party (21 USC 811 (b)).

Schedule I drugs are subject to a near complete prohibition and are only legally available for research under the tightest controls. *The CSA states that a drug may not be placed in Schedule I unless three findings are established. The drug must have a high potential for abuse relative to other controlled substances, no currently accepted medical use in the United States, and lack accepted safety for use of the drug under medical supervision* (21 USC 812 (b)(1)).

Cannabis was placed as marijuana in Schedule I by Congress despite clear evidence it failed to meet these criteria. The Nixon Administration acknowledged that cannabis lacked the dependence liability required for either Schedule I or Schedule II status, but requested that marijuana be placed in Schedule I anyway pending the then-forthcoming work of a national commission on marihuana and drug abuse (Egeberg 1970, 4629):

> Some question has been raised whether the use of the plant itself produces ''severe psychological or physical dependence'' as required by a Schedule I or even Schedule II criterion. Since there is still a considerable void in our knowledge of the plant and its effects of the active drug contained in it, our recommendation is that marihuana be retained within Schedule I at least until the completion of certain studies now underway to resolve this issue.

''Certain studies'' refers to a then forthcoming Commission on Marihuana and Drug Abuse that was mandated with the passage of the Controlled Substances Act (21 USC 801; P.L. 91-513; P.L. 92-13).

This commission eventually recommended the decriminalization of marijuana (National Commission on Marihuana and Drug Abuse 1971).

The National Organization for the Reform of Marijuana Laws (NORML) filed a rescheduling petition in 1972 arguing that marijuana lacked the high potential for abuse required for Schedule I status. The US government refused to accept the petition until so ordered by the US Court of Appeals in NORML v. Ingersoll (497 F.2d 654 (1974)). Subsequently the Court ordered the Drug Enforcement Administration (NORML v. DEA, (559 F.2d 735 (1977)) and the Department of Health and Human Services (NORML v. DEA et al. (1982)) to adequately process the petition. Fourteen years after the petition was filed public proceedings before an Administrative Law Judge (ALJ) were held. By this time the proceedings had narrowed to the single issue of whether cannabis had an accepted medical use (DEA 1986). The ALJ determined that marijuana did have an accepted medical use in the United States and recommended its rescheduling to Schedule II (Young 1988).

Administrative Law Judge Francis Young based his determination that cannabis had an accepted medical use in the United States on a standard adopted from litigation of medical malpractice suits. The burden of proof used in this determination was whether the therapeutic use of cannabis was recognized by a respected minority of the medical community, and Young found convincing evidence in the record that contemporary therapeutic use of cannabis was indeed so recognized (Young 1988).

The DEA rejected Judge Young's standard for evaluating accepted medical use, instituted their own, and declined to accept the ALJ's recommendation; DEA adopted their own standards which relied heavily on journal publication and other commonly utilized scientific criteria (Lawn 1989; Bonner 1992). The Court of Appeals ruled in ACT v. DEA (930 F.2d 936 (1991)) and reaffirmed its decision in ACT v. DEA (15 F.3d 1131; (1994)), twenty two years after the original petition was filed, that DEA's own standards and decision were neither unreasonable, arbitrary, or capricious.

The scientific record in these original rescheduling proceedings closed in early 1989. Later that year a scientific revolution in understanding the effects of marijuana and cannabinoid drugs occurred. Before this time, the scientific basis of marijuana's characteristic ef-

fects was not known. Marijuana's actions have subsequently been elucidated to occur through an endogenous cannabinoid receptor system which has subsequently revolutionized scientific understanding (Howlett et al. 1990; Herkenham 1992; IOM 1999).

The CSA establishes the scope of the scientific inquiry that should be used to determine if a substance meets the requirements of any of the five schedules. The DEA is required to ask DHHS for scientific and medical reviews, and DHHS must consider eight factors in their evaluation. These factors include: (a) the actual or relative potential for abuse, (b) pharmacology, (c) other scientific knowledge of effects, (d) the history and pattern of abuse, (e) the scope and significance of abuse, (f) whether there is a risk to public health, (g) psychic or physiological dependence liability, and (h) whether the substance is a precursor to a controlled substance (21 USC 822 (c)).

As a private citizen the author filed a new petition for marijuana's rescheduling in 1995. This petition argued that the discovery of the cannabinoid receptor system and contemporary findings in each of the eight areas listed above clarified that marijuana does not meet the required criteria for Schedule I or Schedule II status. The petition consisted of an extensive literature review of cannabinoid research findings published between 1988 and 1994. The DEA accepted the petition for filing on July 17, 1995 (Greene 1995) and after extensive review determined that it provided sufficient grounds for removal and rescheduling. In December, 1997 the DEA formally referred the petition to the DHHS for a binding scientific and medical review (Whalen 1997), currently underway.

The results of this review may also require the United States to amend international treaties regarding cannabis in addition to rescheduling marijuana under the CSA. With respect to the scheduling of THC, the active ingredient in marijuana, the US government recognized that the DHHS review process could conceivably require amendment of international treaties (Memorandum of Federal Respondents, NORML v. DEA 1982, 19):

> It is prudent for DDHHS to provide a complete scientific and medical evaluation on THC at this time, because even if the ultimate DHHS recommendation is found to be inconsistent with current treaty obligations, the United States could petition for international rescheduling.

This recognition cites a Court of Appeals Ruling on a prior marijuana rescheduling petition which makes reference to (NORML v. Ingersoll 1974, 658):

> . . . a subsidiary contention that even if there are current treaty obligations, the executive officials have a duty to consider the petition toward the objective of possible treaty modification of legislative or treaty action.

COMMON MISCONCEPTIONS ABOUT MARIJUANA AND THE CONTROLLED SUBSTANCES ACT

The preceding policy context for evaluating marijuana's scheduling under the CSA is frequently misunderstood. Three pervasive fallacies about national marijuana policy in the United States inhibit discussion of the relevance of recent scientific findings. All derive from a failure in the application of the standards for regulating drugs under the Controlled Substances Act. These fallacies make it seem that marijuana prohibition, the status quo, is the only viable policy outcome.

The first fallacy is that any indication that marijuana has a dependence liability justifies its placement in Schedule I of the CSA. The Controlled Substances Act distinguishes the relative abuse potentials of drugs. Schedule IV was added during the legislative process to distinguish the abuse potential of benzodiazepines from that of the barbiturates placed in Schedule III, which in turn are distinguished from drugs such as cocaine in Schedule II, or heroin in Schedule I.

The second fallacy is that marijuana must remain in Schedule I if it has no accepted medical use, and is restricted to Schedule II if it does. In NORML v. DEA (1977) the Court of Appeals held that all three requirements are necessary to justify Schedule I status, and that a drug or substance's potential for abuse is the most important criterion. The highest potential for abuse is also a requirement for Schedule II status. If marijuana does not have the highest abuse potential relative to other drugs it can not be properly scheduled in either Schedule I or II.

In other words court rulings have established that Schedule I is not the default classification for drugs or substances without "accepted medical use in the United States." If it were, the third fallacy would instead be valid, which is that marijuana must remain in Schedule I unless it can be proven to provide optimum results relative to other drugs.

These three fallacies establish artificial standards for evaluating the significance of marijuana research. The first fallacy is the basis for claims that any evidence of dependence liability justifies marijuana's Schedule I status. The second is the basis for assertions that "accepted medical use" is the primary basis for scheduling under the CSA. The third fallacy is the basis for claims that marijuana should be held to a different and higher standard than any other drug in establishing "accepted medical use." All three ignore existing court rulings.

MARIJUANA'S ABUSE POTENTIAL

In the January 1998 edition of the *American Journal of Public Health* Joseph Califano wrote (Califano 1998, 8):

> Recent neuroscientific studies have demonstrated in stunning detail the changes in brain chemistry that marijuana and cocaine cause, opening up possibilities for new treatments. They also challenge old beliefs about the supposed "safety" of marijuana use. The evidence indicates a biomedical link between use of alcohol, nicotine, marijuana, cocaine, and heroin, because all of these substances affect dopamine levels in the brain through common pathways. (Tanda et al. 1998; Rodriguez de Foncesa et al. 1998) Recent research also demonstrates that cessation of marijuana use brings on withdrawal symptoms, which may encourage a user to resume marijuana use or to try other drugs such as cocaine or heroin. (Tanda et al. 1998; Rodriguez de Foncesa et al. 1998)

It has long been recognized that some individuals' use of marijuana is characterized by dependence and that the dependence liability of marijuana is relatively less addictive than alcohol or tobacco, and certainly not comparable to the dependence liability of cocaine or heroin. Despite the importance of the recent scientific breakthroughs in describing how cannabis produces its characteristic effects little has emerged to challenge the conclusions of a frequently cited 1986 literature review by Leo Hollister in the *Pharmacological Review* (Hollister 1986, 17):

> Physical dependence is rarely encountered in the usual patterns of social use, despite some degree of tolerance that may develop . . .

> Compared with other licit social drugs, such as alcohol, tobacco, and caffeine, marijuana does not pose greater risks. One would wonder, however, if society were given a choice based on current knowledge, whether these drugs would have been granted their present status of acceptance. Marijuana may prove to have greater therapeutic potential than these other social drugs, but many questions still need to be answered.

With respect to marijuana, Califano makes a case for CSA control of cannabis but not its Schedule I status. According to Hollister's observation many, though not all, of those questions have indeed been answered by research subsequent to the discovery of the cannabinoid receptor system (see below). It has been long reported that heavy marijuana use followed by abstinence produces a mild withdrawal syndrome characterized by irritability and sleeplessness (Hollister 1986; Abood and Martin 1992; Aceto et al. 1996). Corticotropin-Releasing Factor (CRF) is a chemical released in the amygdala associated with stress and negative consequences of withdrawal from alcohol, cocaine, and opiates (Koob 1996). Rodriguez de Foncesa, Koob, and colleagues have demonstrated that withdrawal from cannabinoids, induced by use of an antagonist to shut down cannabinoid receptor sites in animal subjects, results in the production of CRF (Rodriguez de Foncesa et al. 1998). Billy Martin and colleagues have also used a cannabinoid receptor agonist to produce withdrawal symptoms in animal subjects (Aceto et al. 1996).

This and other research is discussed in a 1998 article in the *Annual Review of Pharmacology and Toxicology* by Christian Felder and Michelle Glass. These authors reach a different conclusion than Califano above (Felder and Glass 1998, 192):

> Much of the political and public objection to the use of ? 9 THC or marijuana as a therapy centers around its abuse potential and the belief by some that it serves as a "gateway" drug leading users to "harder" drugs of abuse. Many therapeutic drugs have abuse potential, yet this does not invalidate their role in current therapies. While there is some preliminary evidence for cannabinoids activating the reward pathways in the brain (Tanda et al. 1998), most investigators have failed to find addictive or reinforcing effects of cannabinoids in animal models. Unlike cocaine or heroin, cannabinoid agonists produce conditioned place aver-

> sion even at low doses (McGregor et al. 1996; Parker and Gilles 1995) and anxiogenic effects (Onavi et al. 1990). Furthermore, animals will not self-administer cannabinoids (Harris et al. 1974; Leite and Carlina 1974; Cocoran and Amit 1974), and a lack of cross-sensitization between cocaine (McGregor et al. 1995) or amphetamines (Takahashi and Singer 1981) and cannabinoids has also been demonstrated.

These statements do not describe a drug with a high potential for abuse comparable to Schedule I or II drugs such as cocaine and heroin. The review of Felder and Glass suggests both that marijuana does not belong in either Schedules I or II, and that it has sufficient therapeutic potential to provide acceptable medical usage. Their analysis confirms what was widely known at the time the CSA was passed and elucidated in the wake of the receptor system discovery.

MARIJUANA'S SAFETY FOR USE

During the 1970's and early 1980's mechanisms by which marijuana caused its characteristic effects were not yet known. According to Miles Herkenham of the National Institute of Mental Health (NIMH) (Herkenham 1992, 19):

> Because the cellular and biochemical mechanisms of action of psychoactive cannabinoids were not understood, neuroscientists were allowed great breadth to speculate upon the influence that these compounds might have on the neurons of the brain.

These speculations were often presented as the latest scientific evidence or as what scientists now believe about cannabis. The perception that marijuana is inherently unsafe for use has a historical basis in this uncertainty about its mechanism of action.

Much speculation was previously based on a theory that cannabis produced its characteristic effects by way of cell membrane perturbation (Paton 1976; Paton 1979; Harvey and Paton 1985), as if the sticky characteristics of marijuana resin actually clogged up circuits in the brain. The persistent yet inconsistent viscosity of cannabinoid resin hampered the experiments. The characteristics of the emulsifiers and the potencies of the tested solutions flawed the research designs in

ways that made their external validity suspect and difficult to interpret (Nahas 1984; Martin 1986; Herkenham 1992).

In 1988 Allyn Howlett and her research team made a key breakthrough thanks to the graduate work of William Devane. Using CP55, 940, a high potency synthetic cannabinoid developed by Pfizer, they were able to establish that cannabinoid effects are mediated by a previously undiscovered endogenous receptor system in the brain (Devane et al. 1989). In the labs of NIMH Miles Herkenham and his research teams mapped cannabinoid receptor locations in the human brain and in several other mammalian species (Herkenham et al. 1990), discovered that tolerance to cannabinoids results from downregulation of receptor sites (Oviedo et al. 1993), and established binding sites in peripheral rat tissues important to understanding cannabinoids' effects on the immune system (Lynn and Herkenham 1992). Rather, cannabinoids produce their action like benzodiazepines and other modern pharmaceuticals that activate or moderate endogenous receptor systems.

Claims that marijuana is a safe drug in terms of accidental overdose were also confirmed by "the paucity of receptors in medullary nuclei that mediate respiratory and cardiovascular functions" (Herkenham et al. 1990, 1936).

THERAPEUTIC POTENTIAL

The distribution of cannabinoid receptor sites provides explanations for many of the therapeutic effects claimed by marijuana users. For example (Herkenham et al. 1990, 1936), "dense binding in the basal ganglia and cerebellum suggests cannabinoid involvement in movement control . . . beneficial for some forms of dystonia, tremor, and spasticity." Yet patients' anecdotes of these and other therapeutic effects were dismissed by the Drug Enforcement Administration (DEA) in 1989 and attributed not to the motor control effects but to the presumed high potential for abuse of Schedule I drugs (Lawn, 1989).

The potential of cannabinoids to relieve pain has been the basis for the development of several synthetic cannabinoid analogs (Segal 1987; Johnson and Melvin 1987; Melvin and Johnson 1987). Recent cannabinoid research findings also report analgesic effects of a cannabinoid agonist on neuropathic pain (Herzberg et al. 1997), relief from migraine symptoms (Russo 1998), significant antinociception from

injected cannabinoids (Smith et al. 1998), antioxidant properties useful as neuroprotective agents (Hampson et al. 1998), pain control resulting from the endogenous cannabinoid anandamide (Calignano et al. 1998), and activation of a brainstem circuit also involved in opioid analgesia (Meng et al. 1998; Martin, W.J. et al. 1998).

The contemporary and historical use of cannabis in a therapeutic and medical context is well documented (Mathre 1997). Contemporary therapeutic use of marijuana is extensively portrayed in *Marihuana the Forbidden Medicine* by Lester Grinspoon and James Bakalar (1997), which includes many case histories of patients discredited by the DEA, and recently vindicated by receptor-related discoveries. The therapeutic potential of marijuana and cannabinoid drugs has been recognized for glaucoma, nausea and vomiting, analgesia, spasticity, multiple sclerosis, AIDS wasting syndrome and several other areas (IOM 1982; Hollister 1986; Howlett et al. 1990; Grinspoon and Bakalar 1997; Mathre 1997; Taylor 1998; Felder and Glass 1998).

The legislative history used by the Court of Appeals to interpret the CSA instructs that the "social, economic, and ecological characteristics of the segments of the population involved" be considered, along with the "economics of regulation and enforcement attendant to such a decision." Also, one "should be aware of the social significance and impact of such a decision upon those people, especially the young, that would be affected by it" (US Code Cong. Adm News 1970, 4603). Therapeutic marijuana use is relevant in assessing the intent of some users and the social costs of prohibition on those that it affects. These considerations can not be omitted from cost/benefit considerations.

The underlying basis for legislative perpetuation of marijuana prohibition under current US law purports that marijuana is too dangerous for individuals to use on the basis of informed consent, and that all marijuana use is the result of risky thrill seeking and drug dependency. It is now evident not only that a majority of people use marijuana on the basis of informed consent but that a considerable number use cannabis in order to utilize its pharmacological effects in therapy for a diverse number of clinical conditions.

CONCLUSION–POLICY RAMIFICATIONS

The Controlled Substances Act was passed with recognition that (21 USC 801 (1)):

> Many of the drugs included within this [Act] have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people.

Of the many policy issues that stem from the Schedule I status of cannabis it is medical access that remains a paramount concern for the public interest. While state law is beginning to provide some protections for medical users of cannabis in several states, medical access is difficult if not impossible without changes in federal scheduling. One purpose of the CSA was to balance the public interest in controlling dangerous drugs with its interest in having the greatest possible access to drugs with useful and legitimate medical purposes.

Acknowledgement that marijuana is not as dangerous as the law once claimed may lead to reconsideration of other marijuana-related laws and policies. It is a betrayal of the public trust to treat cannabis as if it has the same potential for abuse as heroin and cocaine. The substantiation of the scientific basis for US marijuana laws can also enhance the integrity of law enforcement and public health activities and otherwise contribute to their increased effectiveness.

While pharmacological sources for cannabinoids are available now and maybe improved in the future, this matter is irrelevant to the legal issues presented by any individual's marijuana use. In the case of medical use of cannabis the primary public policy issue is whether the state wishes to criminally prosecute individuals whose use of this substance is for therapeutic reasons and a matter of informed consent. Science has established a rational basis for such therapeutic use and clarified marijuana's abuse potential sufficiently to support the ability of individual patients to exercise informed consent about its use. The question is not whether marijuana is the best medicine but whether people who use it medically should be treated as criminals.

Scientific standards provide the best guide to drug control regardless of where they may lead in terms of policy outcomes, because they provide a consistent and reliable basis for rational evaluation and analysis. This was, indeed, the intention of the Congress when it passed the CSA and designated the DHHS as the preeminent judge of scientific fact. Congress intended for the scheduling of drugs to remain consistent with contemporary scientific knowledge. In the case of cannabis, contemporary scientific knowledge does not support its current placement in Schedule I as a drug with the highest potential for abuse.

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BOOK REVIEWS

THE SCIENCE OF MARIJUANA. Iversen, Leslie L. *Oxford: Oxford Press, 2000, 283 pp., $29.95, hardcover.*

This book represents the latest entry in popular texts on cannabis, and is a well-written, inexpensive and accessible review of the important topics. After a brief but insightful foreword by Solomon Snyder, Dr. Iversen, a fellow psychopharmacologist, guides us through discussions of the plant, the pharmacology of THC, and its CNS and peripheral effects. Chapters on medical uses of cannabis, its safety issues, recreational use and future prospects follow subsequently. Iversen presents all topics, including more technical aspects of the endocannabinoids in a clear, measured narrative. In fact, one of the primary strengths of this tome is its thoughtful and well-considered moderate tone in pursuit of controversial topics.

The book is well researched and documented. The references, though not exhaustive, include important representative books and articles on selected topics. The index, in contrast, is somewhat limited.

Other criticisms worthy of mention are very few. A couple of errors rankle: a consistent misspelling of *sinsemilla* (modern term for *ganja,* the unfertilized female cannabis flowering tops, ‘‘without seed’’) as ‘‘sensemilla’’; multiple citations of Abel’s seminal review of cannabis history, *Marihuana: The First Twelve Thousand Years,* as published in 1943 instead of 1973. These are not substantive complaints. More importantly, the wealth of current data on the role of cannabis, endocannabinoids and synthetics on mechanisms and treatment of pain are given a more superficial discussion than this reader would desire. Some clinicians may take issue with Iversen’s contention that the

current armamentarium of anti-anxiety agents and hypnotics, particularly benzodiazepines, has rendered "obsolete" these debated indications for cannabis.

Iversen emphasizes that dangers of smoked cannabis have been exaggerated. Unfortunately, he succumbs to the traditional pitfall of Western pharmacology that dictates that marijuana merely represents a crude vehicle for THC administration. An exploration of cannabis' other important terpenoid and flavonoid components and their interactions with the cannabinoids would be welcome. The German concept of phytochemical synergy is not applied herein to this most complicated herbal medicinal.

Lest anyone consider passing up this fine offering on the basis of these criticisms, they would making a serious error. Iversen's ability to present complex topics in an understandable and compelling fashion is noteworthy. It is truly refreshing to see a thorough airing of the controversies surrounding cannabis in a manner that appears free from any apparent political agenda. Rather, the scientific facts are weighed on their respective merits. In closing, *The Science of Marijuana* is a finely penned and documented effort that deserves a wide reading by scientists, clinicians, politicians and the public.

Ethan Russo, MD

HASHISH! Clarke, Robert Connell. *Los Angeles: Red Eye Press, 1998, 387 pp., $29.95, softcover.*

Rob Clarke, a cannabis researcher with HortaPharm in Holland, and projects manager of the International Hemp Association has written an exclamatory book on hashish, that peculiar Middle Eastern crude extract of cannabis.

Clarke presents an in-depth history and analysis of the topic pertaining to its people, places and techniques. Stunning photos accompany the text, which is well-written, lively and sometimes humorous. Although this book will be of greatest interest to past and present *aficionados* of recreational cannabis, who wish to investigate the THC content of that Afghani hashish that invaded their dorm rooms in the '70's, there is much here of scientific value.

Clarke devotes a great deal of attention to the methods of cannabis processing including rubbing and sieving that concentrate THC and terpenoid cannabis components. A most complete analysis of water extraction techniques, and vaporization methods for smoking cannabis are also included. Medical application is treated briefly.

There is no doubt that some will see this book as subversive and exploitive, the kind of material that many federal legislators would like to render illegal. In this age where some dare to speak about ‘‘harm reduction’’ as applied to cannabis and other illicit drugs, however, Clarke's treatise has much to teach clinical cannabis patients and clinicians, while offering a challenge to interested scientists to further investigate the topic.

Ethan Russo, MD

EDITORIAL

The first article of our second issue brings to us a voice that will be new to many, that of Farid Alakbarov, a scientist/scholar from the newly emerging republic of Azerbaijan. We are extremely pleased that the *Journal of Cannabis Therapeutics* can serve as a conduit through which international knowledge may be broadened. We welcome Dr. Alakbarov's important contribution to the literature.

Father David Deakle was essentially drafted into service as the editor sought a Greek scholar to investigate the meaning of a short passage from antiquity in that language gleaned from a 150 year old text. Simeon Seth's writings on cannabis were among the first in a Western language since the classic era. We are thankful for this first rendering of this significant work in the English language.

The next article is probably among the longest ever submitted to a medical periodical. Certain more cynical readers may wish to speculate that the editor founded this journal merely as a mouthpiece for his own contributions, but this would be inaccurate. *Hemp for Headache* represents an accumulation of material gathered over a period of almost 4 years, designed to provide a reference source that no one individual would likely have the same opportunity to amass. Should other contributors plan similar examinations of cannabis subjects in similar depth, they will be welcomed in this journal.

Our final article pertains to an area of cannabis usage that the

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required number of editorial reviewers accepted as ''therapeutic,'' that is its relation to music, its appreciation and performance, as rendered by Peter Webster. Unusual cannabis-musical interactions were noted from an early date. In 1845, the famed French psychiatrist Jacques-Joseph Moreau de Tours observed (Moreau 1973, p. 38):

> This excessive development of the sense of hearing must be attributed, at least in part, to the powerful influence that music exerts on those who take hashish. Words fail to portray the variety of emotions that harmony can produce. The crudest music, the simple vibrations of the strings of a harp or guitar, rouse you to a point of delirium or plunge you into a sweet melancholy.

So strongly did Moreau believe in the therapeutic properties of cannabis and music that patients receiving it therapeutically were regularly treated to live music concerts at the *Hospice de Bicètre.*

Almost a century later, Walter Straub, a pharmacology professor from Munich commented on the augmentation of musical appreciation under the influence of hashish (Straub 1931, p. 17), ''For the musical person, the noise of a poorly lubricated machine in the laboratory was music;'' This would seem to suggest the aural equivalent of producing a silk purse from a sow's ear. Nevertheless, as was noted (Congreve 1697, Act I, Scene I), ''Music has charms to soothe the savage breast, To soften rocks, or bend a knotted oak.'' The editorial staff agrees, and now others may have the opportunity to judge for themselves.

Ethan Russo, MD
Editor

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Medicinal Properties of Cannabis According to Medieval Manuscripts of Azerbaijan

Farid U. Alakbarov

ABSTRACT. Azerbaijani people have rich and ancient traditions in the medicinal use of cannabis. The traditional methods of its application are described in the medieval Azerbaijani manuscripts in the field of medicine and pharmacognosy written in Old Azerbaijani, Persian, Arabic and date back to the 9-18th centuries AD. As a result of these studies, it was established that various parts (the roots, resin, leaves and seeds) of *Cannabis sativa* L. were widely used in traditional medicine of medieval Azerbaijan. Recently, a number of forgotten recipes of the medicines containing cannabis have been deciphered. These recipes of the Middle Ages may be applied in modern medicine once they have been experimentally and clinically tested.

KEYWORDS. Azerbaijan, cannabis, *Cannabis sativa* L., *Cannabis ruderalis* Janisch., traditional medicine, phytotherapy

INTRODUCTION

Representatives of the plant genus *Cannabis* are common in the mountains, mid and low country of Azerbaijan, especially near rivers.

Farid U. Alakbarov, PhD, ScD, is affiliated with the Institute of Manuscripts of the Azerbaijan Academy of Sciences, 370001, Istiglaliyat Street 8, Baku, Azerbaijan (E-mail: alakbarov_farid@hotmail.com).

Medicinal Plants of Azerbaijan classifies them as various forms of a monotypic genus (Damirov et al. 1988). Other botanists point out that there are two species of cannabis in Azerbaijan: *Cannabis sativa* L. and *Cannabis ruderalis* Janisch. (Rahimov 1961). *Cannabis ruderalis* is considered a wild herb, which occurs in the mountains of the Major Caucasus, Nakhichevan, and is also encountered in wastelands between the Kura and Araks rivers. *Cannabis sativa* is cultivated in these areas for fiber and seeds (Rahimov 1961; Alakbarov 1999).

Over many generations, selective cultivation by humankind led to the evolution of drug and hemp cultivars of this plant. Industrial hemp can be easily distinguished from drug cannabis by appearance, cultivation methods and chemical analysis. It is non-intoxicating, and contains less than one percent tetrahydrocannabinol, while the drug cannabis potentially contains up to 40% or more of this active compound. Currently, industrial cultivation and medicinal application of cannabis are very popular in many countries (Johnston 2000). In Azerbaijan, hemp fiber is used for making tow and oakum fibers, ropes, and sails. Hempseed oil is applied in culinary arts, for technical purposes, in preparation of drying oil, etc. Azerbaijanis consider hempseed-cake a good fodder for domestic animals (Rahimov 1961).

Cannabis has been widely used in Azerbaijan for medical purposes from antiquity. The author of the present study has attempted to collect and analyze the ancient recipes containing cannabis by examination of a number of medieval Azerbaijani manuscripts in the field of medicine and pharmacy that date back to the 9-18th centuries AD. As a result, for the first time, information about cannabis contained in the medieval Azerbaijani sources is available to a wider audience.

MATERIALS

To study the traditional application of cannabis in Azerbaijan, a number of the medieval sources on medicine and pharmacognosy have been analyzed (Alakbarov 1992, 1998). Most attention was paid to the primary sources from the collection of the Institute of Manuscripts of the Azerbaijan Academy of Sciences. This Institute boasts one of the richest collections of medieval writings in the world. There are about 14,000 medieval manuscripts including 390 books in these fields. The information about medical application of cannabis has been collected from the books by Azerbaijani authors of the Middle

Ages. Their works are written in Old Azerbaijani, Persian and Arabic, the literary languages of the medieval Azerbaijan. These sources are as follows:

1. Mu'min, Sayyid Muhammad. *Tuhfat al-Mu'minin* (Gift of Religious Believers). The manuscript of the Institute of Manuscripts (Baku). 1669 AD, Code: M 243/3747.
2. Irawani, Haji Suleyman bin Salman Kajar. *Fawa'id al-Hikmat* (Benefits of Wisdom). The manuscript of the Institute of Manuscripts (Baku). 17th century. Code: B 39/19955.
3. *Tibbnama* (The Book of Medicine). The manuscript of the Institute of Manuscripts (Baku). 1712 AD, Code: C 331/1894.
4. Shirwani, Hasan bin Riza. *Siraj al-Tibb* (Light of Medicine). The manuscript of the Institute of Manuscripts (Baku). 17th century. Code: B 559/2394.
5. Khoyi, Ibn Kabir. *Jam' al-Baghdadi* (Baghdads Collection). The manuscript of the Institute of Manuscripts (Baku). 1311. Code: D 845/9456

These manuscripts have been collected from various regions in the Azerbaijan Republic from private owners, and were copied in our country. These books were widely used by medieval Azeri physicians and may be considered as the most popular medical books of medieval Azerbaijan.

METHODS

Studying the medieval sources on medicine and pharmacy is fraught with numerous difficulties and requires involvement of various sciences. Medieval sources were handwritten in Arabic script employing scientific terminology and concepts of the era. This hampers correct identification and the deciphering of contemporaneous terms for plants and diseases.

This effort has been accomplished by use of modern and medieval dictionaries (Bedevian 1936; Sharaf 1928; Al-Biruni 1973). However, these dictionaries do not always contain necessary information or offer various interpretations of various terms. Fortunately, the medieval manuscripts on pharmacy contain detailed descriptions of botanicals and herbal medicines. The older and modern scientific literature and

reference books on flora (Abou Charr and Ades 1961; Alami 1975; Al-Rawi and Chakravarti 1964; Budge 1913; Damirov et al. 1988; Hakim Mohammed Said 1975; Jayaweera 1980; Kamal 1967; Palewitch 1986; Zargari 1991; etc.) were utilized to assist the author in various stages of this work.

The information on cannabis and its application is scattered in various sources written in different languages, and required great caution and a critical approach to the material, as well as a thorough comparison with the other data obtained on the basis of morphological, ecological and bio-geographical analyses of the plant species described in the medieval sources.

The linguistic material was analyzed as well. For example, there were different words in the medieval Azerbaijani for drug (*bang*, *banj*, *hashish*) and hemp (*kanaf*) varieties of cannabis. Both types were designated in Old Azerbaijani by *kinnab*, which is derived from the Greek *cannabis*. Hemp seed was called *shahdanah* (royal seed). *Bang* and *banj* are derived from the Sanskrit *bhang*, while such terms as *kanaf* and *kinnab* are of Greek origin. *Shahdanah* came to the medieval Azerbaijani from the Persian language. Physicians of those times used also the Arabic name for hemp seed–*habb al-malik* (royal seed). The word *naisha* (joy), used for the dried leaves of cannabis, is of Arabic origin. It is of an interest that the names for opium (*khash-khash*) and cannabis (*hashish*) have a common root: *hashish* is derived from *khash-khash*. Such medieval names as *ganja*, *lutki*, *mudra* and *charas* came in Azerbaijan from India. All these terms were widely used by medieval Azerbaijani scholars.

HISTORY OF APPLICATION

The hemp plant has been cultivated in Azerbaijan from prehistoric times. From the 7th-6th centuries BCE, Azerbaijan was the center of the Zoroastrian religion. The *Zend-Avesta*, the holy book of Zoroastrians contains information about a holy beverage named *haoma*. According to these descriptions, *haoma* was a narcotic and hallucinogenic drink similar to soma of the Indian *Atharva Veda*, used in magico-religious ceremonies of the time. Some scientists hypothesize that *haoma* was prepared from a base of *bang* (dried leaves of cannabis) (Huseynov 1958). However, most authorities believe that *haoma* was prepared with another plant (so-called "haum al-majus" which is

deciphered as *Amanita* spp. or *Ephedra* spp.) (Alakbarov 1999). There is some documentation of medical application of *bang* by Zoroastrians (Russo 1998).

In the 8th-5th centuries BCE, Azerbaijan was inhabited by Medeans, Caucasian Albanians and Scythian tribes (Huseynov 1958). All used cannabis widely to treat various ailments. For example, Herodotus mentions cannabis hemp as being cultivated by the Scythians, who used its hemp fiber for making their garments, and the seeds to medicate themselves in vapor baths (Dymock 1890).

The flowering tops of the female cannabis plants or the resin exuded spontaneously from the leaves and stems under certain climatic conditions were used medicinally or as narcotic. More recently, the powdered leaf is mixed with tobacco and smoked as a cigarette or in a pipe.

In ancient times, Azerbaijani medicine was influenced by Indian and Greek schools. The ancient Indian medical books *Atharva Veda*, *Susruta Ayurveda* and *Charaka Samkhita* were well known in medieval Azerbaijan. Such Azerbaijani scholars of the Middle Ages as Ibn Kabir Khoyi (manuscript 1311) and Haji Suleyman Irawani (manuscript 17th century) often cited these Indian books (Alakbarov, 1999). According to their writings, cannabis was also used medicinally. Its effects on humans were described as excitant, heating, and astringent. It was said to destroy phlegm, expel flatulence, induce costiveness, sharpen memory, excite appetite, etc. According to Mu'min (manuscript 1669), Susruta recommended the use of *bhang* (the Indian name for *bang*) to people suffering from catarrh (p. 605).

Muhammad Fuzuli, the poet of the 16th century wrote a poem named *Bang-u Bada* (''Hashish and Wine'') where he criticized the excessive use of narcotics and alcoholic beverages. The poem is written in the Old Turkic from which the modern Azerbaijani and Turkish languages are derived.

The medieval scientist Muhammad Mu'min (d. 1697) pointed out that there were two species of cannabis in Azerbaijan and Iran: cultivated and wild cannabis (p. 604). Probably, the ''wild'' species of this herb was *Cannabis ruderalis*, while the cultivated was *Cannabis sativa* or *Cannabis indica*.

As a rule, physicians and pharmacists of medieval Azerbaijan and other regions of Orient cited the Greek scholars. For example, Abu Reihan Biruni (973-1048 AD) wrote (Al-Biruni 1973, vol. 1, p. 346),

"Galen says that the leaves of this plant cure flatus, dissolve the flatulent matter and act as desiccatives so much that if a man eats it persistently, his sperm dries up."

Therefore, dried flowering or growing fruiting tops of the pistillate plants were traditionally used in Azerbaijan as medicine. Leaves, seeds and resinous exudations of the three varieties of cannabis were also applied for medical purposes.

The resin obtained from the pistillate plants of medicinal strains of cannabis was known in medieval Azerbaijan as *hashish*. More recently, the dried leaves of cannabis are called *naisha* and *anasha*.

Bang. This plant drug consists of the dried leaves, which are a deep green color and usually broken, so as to form a coarse powder. The odor is peculiar. The leaves have long petioles and are digitate, with linear-lanceolate, sharply serrated leaflets, tapering to a long smooth point. The information about bang is contained in the book by Irawani (manuscript 17th century, p. 232).

Ganja. This is the name given to the flowering tops of the female plant. The flowers form erect clustered spikes that are compressed, flat or round, glutinous, and of a brownish-green color. They have a peculiar narcotic odor (Dymock 1880). This remedy was usually brought to Azerbaijan from Bengal and other regions of India.

Lutki. It is a beverage that was prepared by soaking bang in wine (Zargari 1991).

Mudra. The kind of lutki that consists of bang, opium and henbane (Zargari 1991).

Charas. The concentrated resinous matters extracted from the leaves and flowering tops or agglutinated spikes of *Cannabis sativa* L. It is a greenish-brown, moist, resinous mass, having the peculiar odor of the plant, and consists of resin mixed with trichomes and fragments of the leaf. This remedy was usually brought to Azerbaijan from Sind (modern Pakistan). According to Mu'min (manuscript 1669), charas was widely used in medieval Azerbaijan.

RECOMMENDATIONS ON MEDICAL APPLICATION

In the medieval Azerbaijan all parts of cannabis were used for medicinal purposes. The pharmacists of the Middle Ages pointed out that the roots of cannabis have strong antiseptic and antipyretic properties. As a rule, roots were used in the form of a decoction. Some-

times, prescription specified the grinding of roots to apply as a bandage.

In the folk medicine of modern Azerbaijan leaves of cannabis are used to treat quinsy, urinary diseases and prostatitis.

According to medieval Oriental medicine the properties of cannabis leaves are described as cold and dry in the third degree, that is, stimulant and sedative, imparting at first a gentle reviving heat, and then a refrigerant effect. The drug at first exhilarates, improves the complexion, excites the imagination, increases the appetite, and acts as an aphrodisiac. Afterwards its sedative effects are observed. It may lead to indigestion, wasting of the body, melancholy, impotence and dropsy. Modern studies reveal that cannabis leaves contain mucilaginous matter with antiseptic and emollient properties (Damirov et al. 1988). According to medieval Azerbaijani sources the dosage of leaf decoction for internal use was about 3 to 6 g.

Hempseed was called *shahdanah* in mediaeval Azerbaijan, or ‘‘royal seeds.’’ The seeds are used as bird food in modern times, and when cleaned, are free of THC. The seeds contain a fixed oil used as varnish. According to medieval Azerbaijani medicine, hempseed remedies flatulence, stops nausea and diarrhea, and is diuretic.

Along with hempseed itself, the hempseed oil was also widely used in traditional phytotherapy. According to Haji Suleyman Irawani (manuscript 17th century), it was prepared by pressing fresh seeds of *Cannabis sativa* L. (p. 232). Muhammad Riza Shirwani (manuscript 17th century) wrote that the hempseed oil was applied to treat neuralgia, tumors of uterus, pain in the ears, and external tumors (p. 122). Oil was used in the form of ear-drops and special unguents for healing of internal and external tumors. It was felt that hempseed oil, if applied internally decreased sexual desire in men. According to Ethan Russo (personal communication 2000) this is not documented for fresh, cold-pressed oil, devoid of THC. In medieval times, it is possible that a psychoactive oil was pressed from seeds that were not cleaned thoroughly, resulting in possible impotence, as has been described for drug cannabis when used in very high amounts over long periods of time. Another possibility is that hemp seed oil oxidizes rather quickly to form peroxides and epoxides at room temperature. Consumption of these toxins over time may also result in impotence and other complications.

Some recommendations of medieval authors are given in Table 1:

TABLE 1. Medicinal application of *Cannabis* according to the medieval manuscripts of Azerbaijan

Diseases[1]	Vegetative parts applied	Prescriptions	Medieval manuscripts
Abscesses	roots	apply bandage with decoction[2]	Mu'min,[3] p. 605
Anuria	seeds	drink the seed's decoction	Mu'min, p. 605 Irawani, p. 232
Appetite	fresh juice of leaves	drink after eating	Mu'min, 604
Burns	oil of seeds	apply on damaged skin	Tibbname, p. 67 Shirwani, p. 122
Cold	fresh juice of leaves	drop into nose	Mu'min, p. 605
Constipation of bile	dried leaves	chew	Mu'min, p. 605
Dandruff	fresh leaves	apply the paste of fresh leaves on the head	Mumin, p. 605
Diarrhea	dried leaves	powder, mix with sugar, fry well in ghee, add some black pepper and administer in chronic diarrhea	Tibbnama, p. 77
Dysentery	dried tender leaves	1. mix with poppy seeds and take. 2. mix about 1.5 gr. leaves with a little sugar and black pepper powder and eat	Tibbnama, p. 85
Flatulence	seeds	drink the seed decoction	Mu'min, p. 605
Hemorrhoids	stem and leaves	apply poultice of the plant	Tibbnama, p. 173
Hysteria	leaves	mix with asafoetida and take	Tibbnama, p. 52

Diseases[1]	Vegetative parts applied	Prescriptions	Medieval manuscripts
Inflammation of mucous membranes	seeds	apply embrocation (liniment) of the seed	Khoyi, p. 446
Irritation of the skin	stem and leaves	apply poultice of the plant	Tibbnama, p. 54 Irawani, p. 232
Neuralgias	oil of seeds	apply on the diseased part	Mu'min, 605
Nervousness	leaves	chew or drink decoction of the plant	Tibbnama, p. 74
Quinsy	leaves	gargle with decoction several times a day	Tibbnama, p. 57
Pain in ears (1)	fresh juice of leaves	drop into ears	Mu'min, p. 605
Pain in ears (2)	oil of seeds	drop into ears	Mu'min, p. 605 Khoyi, 446
Photophobia	fresh leaves	apply a poultice of the fresh bruised leaves	Tibbnama, p. 117
Rheumatism	oil of seeds	rub joints	Tibbnama, p. 47
Toothache	roots	rinse the mouth with decoction	Tibbnama, p. 53
Tumors in uterus	oil of seeds	apply on the surface of the tumor	Mu'min, 605
Ulcers	roots	bandage with decoction	Mu'min, p. 605
Vermin	fresh leaves	apply the paste of fresh leaves to the head	Mu'min, p. 605
Vomiting	seeds	drink the seed decoction	Mu'min, p. 605 Shirwani, p. 79
Wounds	powder of leaves	apply the powder to fresh wounds	Tibbnama, p. 45

[1] The names of diseases are taken from the medieval sources and may not coincide with the modern medical terminology.
[2] Medieval manuscripts did not show the exact proportions of compounds in these medicines.
[3] Detailed information about the manuscripts is given in *Materials* and *Methods*.

Information on Side-Effects of Cannabis

Medieval authors point out that excessive use of cannabis resin and leaves produced mental exaltation, intoxication, a sense of double consciousness, and finally loss of memory, gloominess, etc. Muhammad Mu'min (manuscript 1669) wrote (p. 605): "Excessive use of hemp leaves is injurious to organs of sense, liver, stomach, deteriorates color of the face, leads to dropsy, mental disorders, dries the brain, decreases sexual desire and dries the sperm."

A number of scholars pointed out that excessive use of hemp seeds may be injurious to human health. Abu Reihan Biruni (973-1048) who was very popular in medieval Azerbaijan and Central Asia cited the work of Dioscorides (Al-Biruni 1973) (vol. 1, p. 346), "The seeds, if eaten in excess, dry up the sperm. It is better to pour the infusion obtained by soaking the moist seeds in into the ears." According to Mu'min (manuscript 1669), overuse of hempseed led to decreasing sexual ability and ulcers in the bowels. To mitigate these side effects, it was suggested that hempseed be combined with poppy seeds and *iskanjabin* (a boiled mixture of honey and vinegar) (p. 604).

Modern Data on Folk Uses of Cannabis in Azerbaijan

All facts cited were collected by the author on the basis of personal communication with the folk healers from rural areas of Azerbaijan Republic. During the last 70 years, the folk medicine in Azerbaijan had been prohibited by legislation. Therefore, many old practices have already been forgotten. Recently, the laws against folk medicine are not as stringent as 10 years ago, and a folk healer who has a special license of the Ministry of Health may freely engage in the practice of medicine.

In rural areas of Azerbaijan, a hot decoction of cannabis fruits with milk is applied to treat dry cough, chronic bronchitis, laryngitis, whooping-cough in adults, or bronchial asthma. One infuses a tablespoon of seeds in a glass of water (approximately–250 g).

Cannabis leaves infused in *arag* (a strong alcoholic beverage similar to Russian vodka) are used against diseases of the stomach and intestine (2 tablespoons of leaves per 1 glass of *arag*). People use an infusion of hemp seed soaked in wine to treat stomach colic (1-2 teaspoons of seeds per 1 glass of wine).

Roasted seeds are considered a good remedy against helminthosis.

A decoction of seeds and flowers is recommended for treatment of the mild and moderate types of diabetes (1-2 tablespoons per 1 glass of water). Decoctions of flowering tops of female plants, as well as decoctions of seeds are used to prepare compresses for rheumatism. To reduce rheumatic pains, it is recommended to massage a patient with the hemp seed oil.

Leaves threshed in water are used in preparation of compresses against tumors, furuncles and as an anti-inflammatory remedy. It is believed that threshed leaves applied externally are good against snakebites and bites of rabid dogs.

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Hemp for Headache: An In-Depth Historical and Scientific Review of Cannabis in Migraine Treatment

Ethan Russo

ABSTRACT. Cannabis, or "marijuana," has been employed in various forms throughout the millennia for both symptomatic and prophylactic treatment of migraine. This document examines its history of medicinal use by smoking and other methods in ancient cultures, including the Chinese, Indian, Egyptian, Assyrian, Greek and Roman, as well as in the Islamic world, and its subsequent adoption by Renaissance and Industrial Age Europeans.

The most prominent physicians of the age in the century between 1842 and 1942 preferred cannabis to other preparations in migraine treatment, and it remained part of Western pharmacopoeias for this indication throughout the period. The writings of this era are examined in great detail in an effort to emphasize useful medical documentation that has subsequently been forgotten.

In modern times, ethnobotanical and anecdotal references continue to support the efficacy of cannabis for headache treatment, while biochemical studies of THC and anandamide have provided scientific justification for its use via anti-inflammatory, serotonergic and dopaminergic mechanisms, as well as by interaction with NMDA and endogenous opioid systems. These are examined in detail.

The author feels that this collective evidence supports the proposition that experimental protocols of cannabis usage in migraine treatment should go forward employing modern controlled clinical trials.

Ethan Russo, MD, is Clinical Child and Adult Neurologist, Clinical Assistant Professor of Medicine at the University of Washington and Adjunct Associate Professor of Pharmacy, University of Montana, 900 North Orange Street, Missoula, MT 58902 (E-mail: erusso@blackfoot.net).

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INTRODUCTION

Throughout medical history, drugs of choice for various indications have changed by the decade, or in recent times, annually. Once having fallen out of favor, few drugs ever resume a favorable opinion. Only a handful has remained popular for decades.

Modern physicians are not cognizant of the prominence that cannabis preparations once held in the practice of medicine. Its departure from Western formularies was due in part to problems with quality control, but more particularly to political biases. As has been recently stated (Notcutt, Price, and Chapman 1997, p. 551), "Unfortunately, almost no clinical research into the use of cannabinoids for pain relief has taken place, primarily because of the legal difficulties in conducting such trials in patients."

Despite its reputation as a "drug of abuse," far more dangerous medications than cannabis remain in our formularies because of their specific medical indications. Thus, we retain opiates for analgesia, amphetamines for treatment of narcolepsy and attention deficit hyperactivity disorder, etc. Thalidomide, which was banned due to its teratogenic effects, may be revived as a mainstream cancer chemotherapeutic with appropriate safeguards. Even the leech is once more a therapeutic and research tool.

This review will examine the history of cannabis use for headache treatment, along with its scientific basis and possible future as a "new" therapeutic agent. It represents a more in-depth attempt at covering this topic as compared to prior publications (Russo 1998; Russo 2001). A recent purported "comprehensive review" of medical marijuana provided only one brief paragraph on migraine (Gurley, Aranow, and Katz 1998), with no early historical data documenting the extensive use of cannabis in migraine treatment.

The current narrative is divided into sections: The Ancient and Classical Worlds, Middle Ages and Islamic World, Renaissance Europe, Industrial Age Western Medical Usage, Modern Ethnobotanical Data, and Recent Research on Cannabis and Cannabinoids. Discussion will focus on issues of headache and analgesia, while that on

political issues will be cited only as pertinent. Safety issues with respect to cannabis have been discussed briefly in a prior publication (Russo 1998). Reviews may be found in the following (Ashton 1999; Hall, Solowij, and Lemon 1995; Zimmer and Morgan 1997). Extensive bibliographies on cannabis have been published by the United Nations (1965), Gamage and Zerkin (1969), Waller et al. (1976), and Abel (1979). Excellent reviews of "medical marijuana" appear in the literature by Mikuriya (1969; 1973), Grinspoon and Bakalar (1997), Mathre (1997), Zimmer and Morgan (1997), British Medical Association (1997), Zimmermann, Bayer, and Crumpacker (1998), Rosenthal, Gieringer, and Mikuriya (1997), and the Institute of Medicine (Joy, Watson, and Benson 1999).

THE HISTORY AND ETHNOBOTANY OF CANNABIS IN HEADACHE TREATMENT

Archeological records substantiate a longstanding mutual association of man and cannabis. It is a member of the plant family, Cannabaceae, with botanical origin in Eastern or Central Asia (de Barge 1860; Candolle 1886). Subsequent authors have often felt that no truly wild hemp exists at this time, and that all modern strains derive from cultivated forebears whose feral ancestor is now lost. Modern analysis has placed the center of diversity for cannabis in Central Asia, possibly in the Pamir plain (Camp 1936), border regions of Kazakhstan, Mongolia, Northwest China and the Russian Far East (Bouquet 1950), or in the Himalayan foothills (Sharma 1979).

The number of species in the *Cannabis* genus remains controversial. Some botanists retain all members as one polymorphic species, while others (Emboden 1981; Schultes and Hofmann 1980; Schultes et al. 1974) have exhaustively documented three species: *sativa*, *indica*, and *ruderalis*. All specimens contain the psychoactive chemical delta-9-tetrahydrocannabinol (THC) to some degree, generally *indica* being most potent, and *ruderalis* least. Additional taxonomic data of interest, particularly with reference to drug strains/species in Afghanistan (*C. afghanica*), ratios of cannabis components tetrahydrocannabinol (THC) to cannabidiol (CBD), and possible true wild plants, is discussed a book by Clarke (1998).

Ancient and Classical Worlds

It is claimed that cannabis use occurred in central Europe by the Bylony culture as much as 7000 years ago (Kabelik, Krejei, and Santavy 1960). Physical evidence for its early employment in 1896 in Wilmersdorff (Brandenburg), Germany in the form of a funerary urn that contained cannabis leaves and fruit (Busse 1897), subsequently dated to the 5th century BCE (Andrews and Vinkenoog 1967; La Barre 1980). According to Ames (1939), Hartwich (1911) interpreted the urn contents to represent early use as an inebriant.

China

Use of cannabis fibers to make hemp has been documented as early as 4000 BCE in China by Carbon-14 dating (Li 1974), and has been maintained continuously up to the present day. Its seed grain was an ancient human foodstuff, which may have lead to an early recognition of its medicinal use. The first records may occur in the *Pên-tsao Ching*, a traditional herbal written down in the 1st or 2nd centuries, but based on the oral traditions passed down from the Emperor Shên-nung in the third millennium BCE. The text noted that the plant fruits "if taken in excess will produce hallucinations (literally "seeing devils") (Li 1974, p. 446). The *chuan* pictograph for cannabis, or *Ma*, is easily recognized as harvested plants hanging inverted in a shed.

Julien (1849) submitted a controversial report of powdered cannabis use as an early surgical anesthetic in the early 2nd century.

Indications of cannabis for headache do not seemingly appear in China until a later time (see Ethnobotany section).

India

The *Atharva Veda* of India, dated to between 1400 and 2000 BCE referred to a sacred grass, *bhanga*, as an herb to allay anxiety (Indian Hemp Drugs Commission 1894). The *Sushruta Samhita* cites medicinal references to cannabis dating to 600-400 BCE (Sushruta 1991). Dwarakanath (1965) asserted that cannabis has been employed in folk medicine from the 4th to 3rd centuries BCE. He noted Ayurvedic preparations called *Rasachandrika vati* and *Mahalakshmivilasa rasa*, said to contain cannabis indicated for (p. 17), "Diseases of the head

including neuralgic headaches, haemicrania etc. (Shiroaroga) [term for migraine].''

Other authors stated (Muthu 1927) (p. 27), ''The Hindus also used the fumes of burning Indian hemp (*Cannabis indica*) as an anaesthetic at a period of great antiquity . . .'' and (Sanyal 1964, p. 61), ''They also used the fumes of burning Indian Hemps (Cannabis Indica) as an anaesthetic from ancient times . . .''

One controversy frequently discussed in literature on the subject concerns the issue of whether actual smoking as a method of drug delivery occurred in the Old World before the European ''re-discovery.'' In a discussion of Indian drugs including cannabis, Walker (1968) addressed the issue, citing many early medical works [such as the *Sushruta Samhita* (Sushruta 1991)] and a variety of herbs, including those with indication for headache.

A modern observation may address the relative dearth of archeological evidence on the smoking issue. Clarke (1998, p. CS5) has described and illustrated a technique whereby cannabis is sieved to produce resin powder which is hand rolled into a ''snake'' that may be smoked without additional paraphernalia, and potentially leaving nothing but ash.

Egypt

Although many authorities have claimed an absence of cannabis in Ancient Egypt, Nunn (1996) cited six supporting experts that it was employed (Mannische 1989; Ghalioungui 1987; Charpentier 1981; von Deines and Grapow 1959; Faulkner 1962; Dawson 1934) as an agent termed *shemshemet*, administered via oral, rectal, vaginal, and local routes, and by fumigation.

Mannische (1989) also has cited evidence of cannabis use in Ancient Egypt in the Pyramid Texts of the mid 3rd millennium BCE Physical proof includes discoveries of hemp remnants in the tomb of Akhenaten (Amenophis IV) around 1350 BCE, and cannabis pollen in the tomb of Rameses II, who died in 1224 BCE.

Persia

The *Zend-Avesta*, the holy book of Zoroastrianism, which survives only in fragments dating from around 600 BCE in Persia, alludes to

the use of *Banga* in a medical context, which is identified as hemp by Darmesteter (*Zend-Avesta* 1895).

Assyria

Medical use of cannabis in Ancient Assyria has been claimed in numerous sources, though has remained controversial. Thompson (Thompson 1924, 1949) documented 29 citations of cannabis in the ancient Assyrian library of Ashurbanipal. These attested to cannabis' analgesic and psychogenic effects by various methods including fumigation. Citations date to the second millennium BCE and pertain to *A. ZAL. LA* in Sumerian, and *azallû* in Akkadian. Through philological arguments the author concluded (Thompson 1924, p. 101), "The evidence thus indicates a plant prescribed in AM [Assyrian manuscripts] in very small doses, used in spinning and rope-making, and at the same time a drug used to dispel depression of spirits. Obviously, it is none other than hemp, *Cannabis sativa*, L." Specifically (Thompson 1949), hemp, or *azallû*, was employed to bind the temples (possibly for headache?).

Israel/Judea/Palestine

Longstanding debate has occurred as to the veracity of cannabis use in the Bible. Benetowa (1936) proposed its presence on a strong philological basis in a Polish/French paper. Her data was re-presented a few decades later (Benet 1975, p. 40):

> Both in the original Hebrew text of the Old Testament and in the Aramaic translation, the word *kaneh* or *keneh* is used either alone or linked to the adjective *bosm* in Hebrew and *busma* in Aramaic, meaning aromatic. It is *cana* in Sanskrit, *qunnabu* in Assyrian, *kenab* in Persian, *kannab* in Arabic and *kanbun* in Chaldean. In Exodus 30:23, God directs Moses to make a holy oil composed of "myrrh, sweet cinnamon, kaneh bosm and kassia." In many ancient languages, including Hebrew, the root *kan* has a double meaning–both hemp and reed.

To expand on this base, the same etymological roots apply to the word cannabis in Scythian and Latin, *kannabis* in Greek, *canevas* in Old

French, *quannab* in Celtic, and *canvas* in English (cannabis hemp was the original source for canvas material). Additionally, we see *cáñamo* in Spanish, *cãnhamo* in Portuguese, *chènevis* in French, *canapa* in Italian, *khanapiz* in old Germanic language, and *konoplya* in Russian.

Although the issue of its biblical presence has been hotly debated, physical evidence of medicinal cannabis use in 4th century Israel/Palestine was recently discovered (Zias et al. 1993).

Ancient Greece and Rome

The historian Herodotus, circa 450 BCE, described how a Central Asian tribe called the Massagetae on Persia's northeastern border sought an altered state of consciousness as a group experience (Herodotus 1998) (Book 1, Verse 202), with the smoke of the fruit of an unidentified burning plant. Another passage (Book 4, verses 73-75) is explicit in use of the word cannabis in description of a similar ritual performed by the Scythian tribe somewhere north of the Black Sea.

In the 1st century of the Common Era, Dioscorides published his *Materia Medica*, perhaps the first pharmacopoeia in the Western World, describing the analgesic role of cannabis (Dioscorides 1968) (3.165) (p. 390), "Cannabis is a plant of much use in this life for ye twistings of very strong ropes, . . . but being juiced when it is green is good for the pains of the ears."

In the 2nd century, the Greek physician Galen expounded on medical indications, mainly gastrointestinal (Brunner 1973), but also noted of cannabis (Galen) (100.49, p. 350), "If consumed in large amounts, it affects the head by sending to it a warm and toxic vapor."

Subsequently, Oribasius elaborated on this point (Oribasius 1997, Book I, v. 32, p. 65), "The seed of hemp is difficult to digest and bad for the stomach, causes headaches, and is unwholesome; it is somewhat heating." These unsubstantiated side effect claims were to be echoed by Middle Eastern and European authors for some 15 centuries.

The Middle Ages and Islamic World

The medicinal use of cannabis as and herbal treatment or *hashish* has been well documented in early Islamic texts (Lozano Camara 1997). Jabir ibn Hayyan observed a psychoactive effect in the *Kitab al-Sumum* ("Book of Poisons") in the 8th century (Lewis et al. 1971).

In the 9th century, Sabur ibn Sahl, a Nestorean Christian physician in Persia cited use of cannabis five times in his dispensatorium, *Al-Aqrabadhin Al-Saghir* (Kahl 1994, p. 68), the earliest known document of Arabic pharmacology. According to Dr. Indalecio Lozano (personal communication, 2000), ibn Sahl offered four recipes for compound medicines containing cannabis. The third of these comprised a large number of ingredients, and was used to treat a variety of aching pains, specifically migraine and headache. He prescribed that the compound medicine of many items (or *theriac*) be mixed with juice of cannabis (*ma al-sahdanay*) and then should be instilled into the patient's nostril. This represents the earliest unequivocal, direct citation of cannabis use for migraine that the author has been able to document. The prescription dictates administration by a parenteral route, intranasally, which circumvents the oral pitfalls of oral migraine treatment due to the nausea, emesis, and gastroparesis of that disorder.

Abu Mansur ibn Muwaffak in 10th century Persia in his work *Kitab al-abniya 'an haqa'iq al-adwiya* ("Book of the Foundations of the True Properties of Remedies"), described the use of cannabis fiber for making rope, and the plant to treat headache according to two sources (Lewis et al. 1971; Levey, 1973), although a translation of the German text seems to echo Galenic warnings that it produced headache (Kobert 1889).

Cannabis also figured in the medical writings of Avicenna (ibn Sina) in the 10th century, wherein the inebriating effects of the plant leaves were noted (Ainslie 1826), those of Simeonis Sethi, a Byzantine scholar in the 11th century (Sethi 1868), and Maimonides in the 12th century (Meyerhof 1940; Maimonides 1979). Also in the 12th century, Al-Biruni noted (Biruni 1973, p. 346), "Galen says: 'The leaves of this plant [Indian hemp = cannabis] cure flatus–Some people squeeze the fresh (seeds) for use in ear-aches. I believe that it is used in chronic pains.' "

Throughout the Islamic Age, a definite ambivalence reigned concerning cannabis pitting its medicinal effects against its inebriating actions, which were arguably contrary to Muslim precepts. The first known government sanction on cannabis occurred at the behest of King al-Zahir Baybars at the close of the 13th century (Hamarneh 1957). Nevertheless, Umar ibn Yusuf ibn Rasul persisted in suggesting cannabis for ear and head pain (Lewis et al. 1971).

Some centuries later, the use of an electuary named *bars*, or *barsh*,

containing a variety of herbs with or without cannabis, swept the Arab world. Though maligned, and outlawed, it retained numerous medical indications, including treatment of persistent headache (Lozano Camara 1990).

The 17th century Persian medical text *Makhzon-ul-Adwiya*, or *Makhzan al-adwiya*, described cannabis in its various preparations, as an intoxicant, stimulant and sedative, but also (Dymock 1884, p. 605), "The leaves make a good snuff for deterging the brain . . ." This source also recommended a poultice of its boiled roots (Kaplan 1969, p. 175) "for allaying neuralgic pains."

Renaissance Europe

Hildegard von Bingen, the 12th century abbess, musician, and herbalist wrote of cannabis in her *Physica*, stating (Fankhauser 2001, p. 34):

> Whoever has an empty brain and head pains may eat it and the head pains will be reduced. Though he who is healthy and full of brains shall not be harmed by it.–He who has an empty brain shall be caused pain by indulging in hemp. A healthy head and a full brain will not be harmed.

European awareness of the psychoactivity of cannabis was rekindled with the writings of Garcia da Orta, who visited India in the 16th century, and noted its sedative and appetite-stimulating properties in his 1563 book (da Orta 1913).

Contemporaneously, Rabelais wrote of cannabis in his *Gargantua et Pantagruel*, including an excellent botanical description of the plant and its medicinal uses (Robinson 1946; Rabelais 1990). Prosper Alpinus (Alpin 1980) visited Egypt in 1591 and documented the use of cannabis as an inebriant and visionary drug.

Medicinal uses persisted in England. In 1640, in the *Theatrum Botanicum*, *The Theater of Plantes* (Parkinson 1640), John Parkinson indicated (p. 598), "The decoction of the roote is sayd to allay inflammation in the head, or any other part, the herbe it selfe, or the distilled water thereof performeth the like effect;"

Culpeper echoed similar wording in his famous herbal (Culpeper 1994, p. 183), "The decoction of the root allays inflammations of the head, or any other parts; the herb or the distilled water of it, does the same." Other European documentation of psychoactive and medicinal

usage of cannabis was provided by Ange de Saint-Joseph (Ange de Saint-Joseph 1681), Berlu, in his 1690 book, *Treasury of Drugs* (Flückinger 1879), Georg Everard Rumpf (Rumpf and Beekman 1981), Rheede (Rheede 1678-1692), Chardin (Chardin 1711), Engelbert Kaempfer in his *Amoenitatum Exoticarum Politico-Physico-Medicarum* (Dolan 1971; Kaempfer 1996), and Lemery (Lemery 1733).

In his book, *Traité du Chanvre*, Marcandier (1758) noted pertinent inebriating and anti-inflammatory effects of cannabis (pp. 40-41), "Its root, boiled in water, and smeared in the form of a cataplasm, softens and alleviates joints of the fingers that are retracted, It is quite strong against gout, and other swellings of nervous, muscular and tendinous parts."[translation EBR]

Linnaeus cited these uses of *Cannabis sativa* in his *Materia Medica* (Linné 1772, pp. 213-214), "narcotica, phantastica, dementans, anodyna, repellens." This supports the concept that earlier scientists understood not only the psychotropic properties of cannabis, but also recognized its analgesic value. Bergius noted a distinction between the psychoactive effects of cannabis grown in the Orient as compared to European samples (Bergius and Hesselberg 1782).

After the Napoleonic campaign in Egypt, cannabis usage was popularized through the literary works of Silvestre de Sacy (Sacy 1809), and subsequently, Moreau (1845), Gautier (1846), and Baudelaire (1860), patrons of *Le Club des Hachichins*.

Industrial Age Western Medical Usage of Cannabis

The medical use of cannabis, or what became known as "Indian hemp" was reintroduced to the West, yet again, in 1839 (O'Shaughnessy 1838-1840). His treatise on the subject dealt with the apparent symptomatic and analgesic utility of a plant extract administered to patients suffering from rabies, cholera, tetanus, and convulsions.

The earliest specific citation on cannabis use in headache treatment in modern Western medicine seems to be from London (Clendinning 1843), shortly after Indian hemp came to England. He began experiments in 1842 (p. 191), on a "medical man of forty-four;" one may assume, Dr. Clendinning himself. In an initial assay before bed, he slept six hours versus his usual three to four, and suffered no indigestion, nor other bodily derangements. In a second trial (p. 192):

> Being frequently incommoded by rheumatic irritation in the head, producing frightful dreams, troublesome nightmare, megrims [archaic word for migraine], headaches, &c., he took 20 minims of the tincture of hemp, with *3fs*. spir. ammon. arom. at bed time, and with effects similar in kind to those experienced on the former occasion. He has since taken *3fs*. of the tincture, with ammonia, for a similar head affection, and with very satisfactory effect.

Clendinning described his results of treatment with 18 patients, three of whom suffered headaches. In each case, tincture of Indian hemp provided relief, even in cases of morphine withdrawal (p. 209):

> I have no hesitation in affirming that in my hand its exhibition has usually, and with remarkably few substantial exceptions, been followed by manifest effects as a soporific or hypnotic in conciliating sleep; as an anodyne in lulling irritation; as an antispasmodic in checking cough and cramp; and as a nervine stimulant in removing languor and anxiety, and raising the pulse and spirits; and that these effect have been observed in both acute and chronic affections, in young and old, male and female.
>
> In reply to the latter question, I should say that these useful, and in several cases most salutary effects have been obtained without any important drawback or deduction on account of indirect or incidental inconveniences.

Back in India that same year, Shaw (1843, p.77) commented on a patient who had been "in hospital frequently of late with cephalalgic affections induced by intemperance." A tincture of *Cannabis indica* alleviated all his symptoms including an attack of cholera.

In Ireland, Donovan (1845) was effusive in his praise for the new therapeutic tool, summarized results of his colleagues, then described his own extensive trials, mainly in patients with neuropathic and musculoskeletal pain (pp. 389-391):

> The next case is that of a lady who laboured under a severe attack of browach [read "browache"], which for several days had come on a nine o'clock in the morning, and went off about one. "The pain (she described) was not sharp, but heavily intense, with a slight throbbing." She tried several remedies in vain; at length I

> directed her to take three drachms of tincture of the herb [cannabis], about one hour before the accession of the pain. The following is her own account of the effects, written at may request:- "Although feeling giddy, and indisposed to exertion, I got up an hour after taking the medicine, and went down stairs a little unsteadily. During breakfast I felt my head occasionally nodding, in that sudden way which one experiences while dozing in a chair . . . I had next to no pain over my eye, yet was constantly putting up my hand to where the pain had been; my reason as constantly telling me the pain was gone. . . . finally, after dozing a few minutes, awoke quite well about four o'clock. I have not had any return or tendency to return of the pain."
>
> Dr. Graves by accident saw this lady in the singular state above described. Notwithstanding her apprehensions, she in a day or two after called on me to inquire if she should take more of the medicine, with a view to securing herself against a return of the browach; but of course none was given her.
>
> The next case was that of William Dunn, a stout peasant, living near Slane, subject to a violent pain in the head, which attacked him at intervals of about a month.

This gentleman was also administered tincture of Indian hemp resin. He experienced a variety of unusual bodily sensations, some arguably due to the prescription, others likely secondary to the migraine (p. 391):

> ". . . He thought his eyes would burst out of his head; and that he would be bruised, and blown up the chimney. Every thing appeared very bright. Then he would bet a few moments' ease when it would commence its rig again." This lasted about three hours and a half, during which the pain was not felt, but then returned a little. Finally, he fell asleep; slept eight hours, and was perfectly well, except that he was "weak and dull." The poor man's alarm was so great that he sent for his priest; but this did not prevent his coming to Dublin for another dose against his next attack.

In neither case were the parties totally dissuaded from subsequent pursuit of this new remedy on account of possible side effects. Donovan described two other cases pertaining to headache. In one, it was

one of a constellation of symptoms relieved by cannabis. In the other (p. 394):

> The case of the Reverend R. H–11, is thus stated by himself: the tincture of Indian hemp was prescribed for him by Dr. Aickin: "I had so bad an attack of pain in the head (to which I have been subject for some years), that I resolved to try your dose. The pain was so acute at one side of the forehead, that it awoke me before day-light, and continued unabated until about half an hour after I took the Indian hemp, when the pain gradually died away. The only effect produced beside this was a drowsiness which lasted all the day, during the greater part of which I slept, with out at all interfering with my night-sleep, which was, perhaps, rather improved by it. I also remarked, that instead of having some remains of the pain and weight in the head, as at other times, after a severe attack the pain was gone completely, and left no uneasiness after it."

Donovan summarized with the following comments (p. 399):

> In the foregoing details, I have not made a *selection of the successful cases out of many*, but have faithfully recorded *all* those that come under my observation, of which the termination was distinctly known. It may be seen that far more than the majority of them were cured evidently by the agency of the hemp, and that all the rest were more or less relieved.

That same year, two cases of chorea with headache were described (Taylor 1845). One case was associated with mitral valvular disease, (likely Sydenham's post-streptococcal chorea), while the other might have been due to that disease, trauma or functional causes. All headache symptoms were alleviated by tid dosing with tincture of *Cannabis indica*.

Christison (1851) reviewed the topic of Indian hemp at length. In addition to endorsing its benefits in treating tetanus, and augmenting labor, he reported marked benefit in treatment of neuralgic pain, which many authors of the time conceived of as including migraine.

In 1855, G. Martius published a German essay with an extensive bibliography of medicinal properties of cannabis (Martius 1855).

In 1860, an American doctor stated (Owen 1860, p. 281), "Canna-

bis Indica, when properly administered in small doses, serves to strengthen the constitution, affords an increase of mental activity, and increase of appetite, enables one to endure fatigue, alleviates pain . . .''

Over the next decades, authorities recognized cannabis as helpful for various conditions, including headache. John Russell Reynolds was eventually to become Queen Victoria's personal physician. He reported his successes with Indian hemp (Reynolds 1868). Several of his patients suffered headaches, whether due to migraine, syphilis, or spasm, but all obtained benefit in his hands. One misused the prescription Squire's extract (p. 154):

> A young lady, whose violent head-aches had been much relieved by doses of gr. 1/3, repeated a dose too soon, felt almost immediate freedom from pain, and started with some friends to a white-bait dinner at Blackwall. Unaccustomed to the steam-boat, to whitebait, and to wine, she shortly began to be extremely lively in conversation, then to ''clip her words,'' and suffer from confusion of vision; but whether in this case the result was due to previous head-ache, to the steam-boat, to whitebait, hock, or Indian hemp, I could never satisfactorily determine.

In another case, there were no such misadventures (p. 19):

> A young lady, age 19, of highly nervous temperament, but with no evidences of hysteria, has suffered from attacks of hemicrania, of great severity, for a period of 18 months. Change of air, various tonics, and alteratives have been tried without avail. The attacks are of almost daily frequency, the general health has become enfeebled, she dreads every kind of exertion and amusement for fear that it should induce the pain. Cannabis Indica was given in gr. 1/3 doses, thrice daily, and after the second day the attacks may be said to have completely ceased; for there have not occurred more than two since that time, and these in each instance arose from the sudden discontinuance of the medicine. It is now more than 14 months, and no medicine has been taken for the last eight.

Reynolds theorized (p. 160):

> This medicine appears capable of reducing over-activity of the nervous centres without interfering with any one of the functions

> of organic, or vegetal life. The bane of many opiates and sedatives is this, that the relief of the moment, the hour, or the day, is purchased at the expense of to-morrow's misery. In no one case to which I have administered Indian hemp, have I witnessed any such results.

Another contemporary citation is that of Anstie (1871, p. 190):

> From 1/4 grain to 1/2 grain of *good* extract of cannabis, repeated in two hours if it has not produced sleep, is an excellent remedy in migraine of the young. It is very important in this disease, that *the habit of long neuralgic paroxysms should not be set up;*

Richard Greene was widely recognized for advocating the prophylactic treatment of migraine with daily doses of *Cannabis indica*. His experience over two years caused him to label it (Greene 1872, p. 267) "nearly always productive of more or less benefit to the patient." He presented six case studies with impressive responses. The two least responsive patients seemed to be non-compliant with the daily regimen. One, however, successfully treated acute migraine attacks with a double dose of cannabis. The other incomplete response (p. 268) occurred in an, "inveterate tea and coffee drinker [who] could by no means be persuaded to give up the use of these wretched stimulants." Thus, from an early date, Greene was able to note the effect known to contemporary neurological practice as "analgesic rebound," that is the tendency of certain agents, when used habitually to perpetuate rather than abrogate chronic headaches.

Overall, Greene stated of his case studies (pp. 269-270):

> These will show that though Cannabis Indica may often fail to cure, it scarcely ever fails to effect some improvement even in the most apparently hopeless cases; . . . this drug may be taken for very many months in comparatively large doses without producing any unpleasant effects or in any way injuriously affecting the economy. . . . As a rule, it will be sufficient to prescribe one-third of a grain [of the alcohol extract] every night or every night and morning, and it may be increased to two-thirds of a grain. . . . In the above cases, however, no drug whatever was used excepting the Cannabis Indica.

In the same journal, Anstie (1872) also recommended Indian hemp for acute migraine relief in a lecture on its treatment.

Liveing (1873) was the author of a popular book on migraine, but failed to mention cannabis as a treatment modality. Despite positive review the next year (Allbutt 1874), the following criticism was offered (p. 319), ''If we discover anything lacking in this book it is in this chapter [on migraine treatment], where Dr. Living, instead of being always better informed than ourselves, seems scarcely more than abreast of the general knowledge on the subject.'' Allbutt then proceeded to fill in the gaps on treatments that deserved greater investigation and endorsement, ''Nitrite of amyl is one of these, and one from which I have been led to hope something; others are ergot of rye, cannabis indica, and digitalis.''

The noted American neurologist, Silas Weir Mitchell espoused cannabis for migraine (Mitchell 1874, p. 70):

> It is necessary at times to do something to give immediate relief to the too prolonged pain, and in these cases a combination of cannabis indica and morphia answers very well; but in a disease so wearisome and long, it is well to be more than cautious in ordering narcotics.

Also in 1874, a popular textbook, *Practical Therapeutics* stated of cannabis (Waring 1874, p. 159):

> Of a good extract, gr. 1/4 to gr. 1/2, rarely gr. j, in the form of pill, is very effective in some forms of neuralgia, particularly *Clavus hystericus* [a lancinating type of pain along the sagittal aspect of the head] and *Migraina*. Even in the severest and most intractable forms it often palliates greatly. It should be given every night, whether there be pain or not.

These continued claims support both acute and prophylactic indications of cannabis for migraine.

Edouard C. Seguin, the President of the New York Neurological Society, gave a speech espousing the preventive benefits of cannabis for migraine that was frequently cited for the next 40 years (Seguin 1878, 1877). To quote (p. 1):

> Briefly stated my thesis is THAT BY THE LONG-CONTINUED USE OF CANNABIS INDICA, MIGRAINE OR SICK-HEAD-

> ACHE MAY BE CURED, MUCH RELIEVED, OR MIGIGATED IN SEVERITY.

Seguin indicated that he had applied techniques suggested by Greene in the intervening several years, and with good success. He felt this approach unique in (p. 4), "treating the disease, of the supposed fundamental pathological state in the nervous system." In comparing cannabis to alternative treatments, he stated (p. 5), "I never allow my patients to take opium or morphia themselves in this disease." His approach to migraine was as follows (p. 6):

> The principle of the treatment is to keep the nervous system steadily under a slight influence of cannabis for a long period of time; . . .
>
> I give adult females one-third of a grain of the alcoholic extract of cannabis indica before each meal, increasing the dose after a few weeks to one-half grain. Males can generally begin with one-half grain, and it is well to give them three-quarters grain in two or three weeks. These doses must be taken with the greatest regularity, just as faithfully and regularly as bromides in epilepsy. Indeed, when beginning such a treatment, I usually obtain a promise from the patient that he will regularly take the pills for a period of three months.
>
> As a rule, no appreciable immediate effect is produced by the above doses, though I have known lightness of the head and slight confusion of mind to result from an initial dose of one-half grain three times a day.
>
> Under this apparently and essentially simple plan of treatment, I have known what may be termed excellent results to be obtained. . . . I feel certain that about one-half of my cases have been relieved. . . . The majority of patients relieved have obtained months of freedom from attacks while taking the remedy.

Seguin's rare document was reviewed the next year in the *British Medical Journal*. The article contained direct quotations and comments (Anonymous 1879):

> When we consider the vast aggregate of suffering which this malady occasions, and, we fear we must add, the unsatisfactory methods of treatment hitherto proposed, at least in many of the

> severer forms of the affection, where relief is most urgently called for, we think Dr. Seguin's concluding appeal to his professional brethren ''to give the cannabis treatment of true migraine a critical trial,'' is abundantly justified.

Day (1880, p. 312) expounded on headaches in a book of the era. Diagnostic categories for its presentations were quite distinct from those recognized today: Day barely mentioned migraine. Nevertheless, ''tincture of cannabis indica'' was prescribed in association with ''the headache of cerebral hyperaemia'' and ''neuralgic headache.''

In the French literature, Michel (1880) extensively reviewed and endorsed the success of cannabis in treating neuralgic afflictions.

Lothrop (1880) reported on the benefits of cannabis in persistent hemicrania. After paying homage to Greene and Seguin, he indicated the principle of treatment (p. 200):

> What the bromides and belladonna are to Epilepsy, cannabis indica is to migraine; not that either of these medicinal agents or any combination of them will cure every case that may come under observation, but they will relieve many. . . . Success here is only obtained by persevering effort. Failure is often complained of, when on inquiry the agent has not had a fair trial;

He offered a case study (p. 201):

> A case is in hand in which hereditary influences bore a prominent part in its causation; in which the skill of the most eminent men in the metropolis had failed to afford any relief, the patient finally resigning herself to the suffering which seemed inevitably to be entailed upon her at each menstrual epoch, the only hope of relief being in the approach of the climacteric which was many years in the future. Hemicrania in its severest form, with nausea, insomnia always followed each menstruation. Life was indeed burdened with the anticipation fulfilled with never-varying certainty of two or three days in each month of suffering from which there seemed no escape, and hence no relief. The prolonged use of cannabis indica of the period of one year, has afforded such relief that the nervous system has had time to regain long-lost vigor, and the patient is in better health than for many years. Other cases might be cited confirmatory of the utility of the agent. Is

> the question asked, Has the remedy ever failed in my hands? And I can answer that it has not in any case in which its prolonged use has been made. The trouble is in the want of perseverance to the patient, not in the efficacy of the remedy.

A self-styled "Country Doctor" stated of *Cannabis indica* treatment (Anonymous 1883, p. 992), "Last winter I had four patients, who found a one grain dose of the extract quite specific in warding off attacks of migrainous headache. For months this had been the case." Another observed (Lawrence 1883, p. 177), "undoubted value which attaches to cannabis Indica in megrim, . . ."

Spender (1884) felt that newer was not always better (p. 1145):

> But I wish to lay special stress on the prophylactic treatment of migraine. Before the days of chloral and the bromine salts, Indian hemp was much more in fashion than it is now; and I often recommended a dose of Indian hemp and of quinine to be taken every night during the intervals of the neuralgic attacks. It is doubtful whether any combination of more modern drugs promises better successes; and we must remember that our aim is gradual alleviation rather than sudden cure.

In a review of headache (Sinkler 1886), in relation to migraine treatment, the author stated (pp. 413-414):

> Cannabis indica is probably the most potent remedy which is at our command. Its effects are most decided, and many cases of hemicrania have been cured by this means alone. It must be given for a long time, and in some instances it is necessary to give gradually-increasing doses up to the physiological effects. The drug must be of good quality, otherwise we need expect no good from it. . . . Occasionally, an impending attack can be warded off by the administration of caffeine, guarana [caffeine-containing seed extract of the Amazonian tree, *Paullinia cupana*], or cannabis indica. Cannabis indica may be given in doses of a quarter of a grain of the extract every two hours until relief is obtained.

Sydney Ringer, the inventor of the physiological intravenous fluid that bears his name, devoted a book chapter to the plant (Ringer 1886, p. 562):

> Cannabis indica is one of the most valuable remedies for megrim or sick headache. It appears to act on the nervous centre whence this headache springs. It is found serviceable both in cases associated with little or no nausea, and in cases accompanied by severe vomiting. It is useful in attack accompanied with spectra [visual disturbance in migraine]. It is most useful, in my experience, in preventing the attack, not in arresting them when once they have begun. It is sometimes useful in those severe continuous forms of headache lasting for weeks; but it is especially effective when from fatigue, anxiety, or change of life the attacks become much more frequent; then the drug gradually, and indeed sometimes quickly, lengthens the interval, and at last brings back the attacks to their old periodicity, or even extends the intervals between the seizures. It need hardly be said that cannabis will not cure these patients. I have given this drug weeks or months continuously, in dosed of one-third to one-half grain twice or thrice daily. . .
>
> Subsequent experience has fully confirmed the favourable opinion of it just expressed; no single drug have I found so useful in migraine. . . . Not only is cannabis indica useful in the inter-paroxysmal period to prevent headaches, but a third to half a grain of the extract given at the commencement of an attack will sometimes cut short the paroxysm.

Hobart Hare published an article that dealt with the indication of cannabis for migraine treatment in detail (Hare 1887, pp. 225-226):

> CANNABIS INDICA has been before the profession for many years as a remedy to be used in combating almost all forms of pain, yet, owing to the variations found to exist as to its activity, it has not received the confidence which I think it now deserves. At present certain improvements made in the method of obtaining the extract from the crude drug have very materially increased its reliability, so that by selecting an article made by a responsible firm we may be fairly sure of receiving a preparation in which we can place confidence. Within a few years this drug has become particularly prominent in connection with its use in migraine, particularly when used in conjunction with gelsemium [*Gelsemium sempervirens* (L.) Ait. Loganiaceae, yellow jessamine. This is now recognized as toxic, but is retained in some

modern homeopathic remedies.], although of the two remedies the hemp is by far the most active agent in subduing the pain and preventing other attacks.

. . . I have certainly seen very severe and intractable cases of migraine successfully treated by this remedy, not only in regard to the attack itself, but by acting as a prophylactic. The best use of the remedy under such circumstances is as follows, in case the drug obtained be fairly active. If the attacks are frequent then the remedy should be used constantly in small doses, in such a way that the patient is not conscious of any influence of the drug, and about 1/8 of a grain of the solid extract may be taken night and morning, or, if this produces any tendency to sleep, the whole amount may be taken at night. At the beginning and during the attack it should be freely administered, until either the pain is diminished or very marked symptoms of its physiological action assert themselves; and that this line of treatment is not one calculated to produce serious results is proved by my own experiments, and by the fact that so far no case of fatal poisoning from its ingestion has been recorded as occurring in the human being.

. . . Cases of migraine treated in this way, when the disease does not depend on any distinct organic lesion, are in a large proportion of instance either entirely cured or greatly benefited, the attacks even when they recur being considerably farther apart.

. . . The advantages in its use over that of opium consist chiefly in the absence of prostration and nausea after its ingestion, and in the partial lack of soporific power which it possesses as compared to the opiate, for in certain cases sleep is not always desirable when pain is to be removed. That cannabis indica has, however, marked powers as a soporific is not to be denied. Added to these advantages is the fact of its failure to produce serious symptoms even if very large doses be taken, although I have found the efficient dose of a pure extract of hemp to be as powerful in relieving pain as the corresponding dose of the same preparation of opium.

. . . During the time that this remarkable drug is relieving pain a very curious psychical condition sometimes manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and

> less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing.

Stephen Mackenzie stated (Mackenzie 1887, p. 97):

> Indian hemp is well known as a sedative, and enjoys a considerable reputation–not so large, however, as is deserves–in the treatment of headache. . .
>
> The headache to which I wish to draw attention is of a dull, continuous, or subcontinuous character, attended sometimes with paroxysmal exacerbations.

Mackenzie went on to describe this syndrome at length. It is this author's opinion that he was describing "chronic daily headache," an evolutive subset of migraine. Mackenzie felt of Indian hemp, "In the majority of cases, it cures the complaint." Once more, he employed an alcohol extract, in doses similar to those above cited (p. 97):

> Given in these doses, usually no inconvenience is experienced by those taking cannabis indica; but a few patients have complained of a feeling of slight confusion or giddiness, not in any way so annoying as the condition for which it was administered.
>
> The length of time over which treatment has to be continued varies in different cases; usually, it extends over several weeks, but rebellious cases may require a treatment of two or three months. As the malady recedes, the dose should be reduced, and it is advisable to continue the administration of the remedy for a week or two after the headache has disappeared.

Four case studies were described at length, one that of a medical student who pursued the Socratic method (p. 98), "He has since himself administered the drug to others suffering in like manner."

The following year, Greene (1888) opined that Indian hemp had not received its due recognition in migraine treatment, particularly in England. He revisited the topic with the benefit of 16 years of additional usage, "Since 1872 I have often prescribed it, and I have yet to meet with a case in which at least some improvement does not follow the careful and continuous use of the drug." He cited 3 representative cases (p. 36):

> Case I.–A female, aged fifty-three. Has been a martyr to this disease for twenty-five years; the attacks recurring very frequently. It was rare that eight days passed without one. In this case improvement began almost immediately; and the attack are not only less severe, but are reduced to once a month.
>
> Case II.–Female, aged thirty-five. Had suffered from migraine for twelve years. She did not remember during that time ever being three weeks without an attack, and was ill of three days. Her, too, improvement began very soon after the treatment, and in eight weeks she considered herself cured.
>
> Case III.–Female, aged thirty-seven. This patient has had sick headache for many years. The attacks came on weekly, and lasted two days. After a few weeks' treatment she was much better, and has now been months without an attack.

Greene commented (p. 36):

> It should be noted that the treatment here advocated afresh is not merely a palliative one during the paroxysm, like the use of guarana, caffeine, hypodermic morphine or nitrite of amyl inhalations, but is often curative and nearly always gives some lasting relief.

He chose to differ with Seguin (p. 37), "In reviewing both, I am confident that in my hands recovery has more frequently followed cannabis indica in migraine than bromides in epilepsy." Greene reiterated his observation of the safety of cannabis and his dosing regimen suggestions over the long term (p. 37):

> when decided relief is felt there is not much fear but that perseverance in the treatment will follow the improvement, as migraine is the reverse of a pleasant companion, and often unfits its victim for an active life several days in every month.

A doctor in India wrote of *Cannabis indica* (McConnell 1888), and how proper storage was key to therapeutic response (p. 95):

> Where care is taken in this respect, the therapeutic value of the drug in certain affections of the nervous system–tetanus, neural-

> gia, migraine &c.–and its powerful effect in controlling uterine haemorrhage (menorrhagia, &c.) has been repeatedly recorded by competent observers, and its employment for the relief of such affections is well understood and more or less extensively resorted to.

William Gowers was one of the founding fathers of modern neurology. For treatment of migraine, he wrote (Gowers 1888, p. 1188), "Most relief is afforded to the pain by a good dose (thirty or forty grains) of bromide, and its effect is increased by the addition of five or ten minims of tincture of Indian hemp." For treatment of "headache," he stated:

> Sedatives are very uncertain in their influence. Opium and morphia are seldom useful, and often do more harm than good, in consequence of the indirect effect of the constipation that is produced. Gelsemium and Indian hemp frequently lessen the pain, the former chiefly in neuralgic forms about the front of the head, the latter not only in neuralgic, but in anaemic, and also other ill-defined forms of headache.

Little (1888) recommended for "migrainous headache" fresh air, exercise, healthy diet, bathing (p. 56):

> And among drugs the combination which has appeared to me to do most good is a pill containing one-twelfth of a grain of arseniate of sodium, one-sixth of a grain of extract of indian hemp, one-third of a grain of extract of bella-donna, and two grains of valerianate of zinc, taken after breakfast and dinner.

Farlow (1889) discussed use of rectal preparations of cannabis (Farlow 1889). Although many of the author's concepts concerning the pathophysiology of gynecological problems seem quite dated a century later, he stated (p. 508), "Cannabis has few equals in its power over nervous headaches such as women with pelvic troubles are subject to."

In India, Watt attributed the following quotation on cannabis to a Dr. E. G. Russell in Calcutta (Watt 1889, p. 124), "Valuable as a remedy for sick headache, and especially in preventing such attacks."

In the USA, Wharton Sinkler (Sinkler 1890) once again reviewed

migraine for a medical newspaper. He observed an unusual feature of the disorder, its tendency to afflict some sufferers weekly on the same day (p. 57), "Cannabis indica was given in increasing doses and the patient was greatly relieved. The periodicity of the attacks was broken up and the intervals became from eight to ten weeks." In another case, he documented (p. 57):

> I gave him cannabis indica and regulated his diet and the attacks were very much relieved in frequency and severity. The Sunday attacks recurred for about nine months. . . . He now very rarely has attacks and they are not so severe as formerly.

Sinkler summarized (p. 59):

> Cannabis indica, which has been given in migraine for many years, still holds a prominent place among the medicinal agents used in its treatment. For myself, I may say that I consider it of more value in the majority of cases of migrainous headache than in any other headache. It must be given for some length of time and the dose should be increased until slight toxic symptoms are felt.

A few weeks later, in the same journal, Aulde (1890) affirmed the prophylactic benefit of extract of Indian hemp in frequent migraine, but reminded readers of its utility and efficacy in acute settings (p. 118), "For the emergency, to relieve the pain and place the patient in a favorable condition, I cannot speak too highly of an assayed preparation of cannabis indica . . ." His patient had suffered inexorably from a three week attack.

Tirard (1890) commented on "toxic effects" of cannabis (p. 723). His case pertained to a 48 year-old man prescribed the tincture for "migraine and lassitude." The same day, Dr. Tirard was summoned to see the patient for anxiety symptoms, after ingesting some 2 1/2 times the prescribed dose. Nevertheless, the patient was easily reassured, and it was reported, "He has since taken the ordinary dose on several occasions, not only without any toxic effects, but with marked relief of migraine and of the ordinary symptoms of business worry."

Benefits of cannabis were also reported in France (Lailler 1890), including its use in migraine.

The *Lancet* published an article on *Cannabis indica* by J. Russell

Reynolds 22 years after his initial report (Reynolds 1890), ''Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess.'' In relation to its use in headache, Reynolds said, ''Migraine: Very many victims of this malady have for years kept their suffering in abeyance by taking hemp at the moment of threatening, or onset of the attack.''

In Germany in 1890, a commercial product was marketed called *Migränin* containing 1% cannabis extract and unspecified active organic substances (Fankhauser 1996, p. 163).

In the following year, the *British Medical Journal* published a short report, ''On the Therapeutic Value of Indian Hemp'' (Suckling 1891), which stated (p. 12):

> In migraine the drug is also of great value; a pill containing 1/4 gr. of the extract with or without a 1/4 gr. of phosphide of zinc will often immediately check an attack, and if the pill will be given twice a day continuously the severity and frequency of the attacks are often much diminished. I have met with patients who have been incapacitated for work from the frequency of the attacks, and who have been enabled by the use of Indian hemp to resume their employment.

In *A Text-Book of Materia Medica and Therapeutics* (Cowperthwaite 1892), once more *Cannabis indica* was indicated for migraine treatment.

The same year, it was written of cannabis (Mattison 1891) (p. 266), ''. . . its most important use is in that opprobrium of the healing art-migraine.'' Mattison paraphrased the work of many authors on the subject as above presented, but then drew from his own experience (pp. 270-271):

> Failure with hemp is largely due to inferior preparations, and this has had much to do with its limited use. It should never be called inert till full trial with an active product proved it. . . . In headache, periodical or long continued, one half to two grains solid extract may be given each hour or two till the attack is arrested, and then continued in a similar dose, morning and night, for weeks or months. It is important not to quit the drug during a respite from pain.
>
> I close this paper by asking attention to the need of giving

> hemp in migraine. Were its use limited to this alone, its worth, direct and indirect, would be greater than most imagine. Bare in mind the bane of American women is headache. Recollect that hemp eases pain without disturbing stomach and secretions so often as opium, and that competent men think it not only calmative, but curative. Above all remember the close genetic relation of migraine relieved by opium, to a disease that spares neither sex, state nor condition.
>
> . . . Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence.
>
> My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic.

Mackenzie (1894) reviewed an additional seven years of cannabis in headache treatment in a French journal (pp. 399-400):

> It exerts a favorable action in all forms of headache, whether of a purely functional nature or due to an organic affection. Thus, I have often succeeded in completely calming by Indian hemp the violent headaches occasioned by brain tumors. In these cases, sometimes *Cannabis indica* acts altogether better than morphine administered by subcutaneous injection, sometimes it is inferior to it as an analgesic. It may interrupt at its debut, or when it has persisted a certain time; its prolonged usage is capable of diminishing the frequency and intensity of the migraine attacks.
>
> . . . I have convinced myself that *Cannabis indica* calms well the cephalic pains of chronic uremia.
>
> . . . In some twenty years that I have employed Indian hemp, I have registered very few failures in the treatment of the particular form of cephalalgia that I have come to describe [chronic daily headache]: I may likewise say that the success of this treatment has been striking precisely in the most inveterate and seemingly particularly rebellious cases.
>
> . . . The feeble symptoms of intoxication sometimes provoked by Indian hemp need not cause us to renounce the use of this precious medicament. In effect, a long experience has demonstrated to me, I repeat, that these accidents are absolutely excep-

> tional. They result either from an idiosyncrasy, or variability in the grade of the drug in its active principle. [translation EBR]

Cannabis in its various forms remained the focus of intense debate. Because of concerns of its dangers, the British and colonial authorities in India organized the Indian Hemp Drugs Commission (1894) to examine all aspects of the issue. Its members, after exhaustive investigation and testimony exceeding 3000 pages, found no reason medically or economically to outlaw the plant or its use. Two pertinent excerpts follow (Kaplan 1969, p. 176, p. 483):

> Witnesses refer to the use of the drugs [*bhang*, *ganja*, *charas*] in the treatment of "brain fever," cramps convulsions of children, headache, hysteria, neuralgia, sciatica, and tetanus.
>
> . . . *Tinctura Cannabis Indicae*
> . . . Sedative, anodyne, and hypnotic, has been used with success in megrim and delirium, also in menorrhagia and dysmenorrhoea.

Brookes (1896) continued to tout cannabis in migraine. His patient was a young woman who suffered severe attacks every one two weeks. He place her on a prophylactic daily regimen as previously recorded (p. 338):

> This treatment has been carried out with the strictest regularity nearly two months, during which period the patient has been absolutely free from a recurrence of pain. . .
>
> I may add I observed no dizziness, or any constitutional derangement, either at the beginning of treatment or during its course.

That year, a brief case report documented a self-limited case of cannabis overdose in a 12 year-old (Attlee 1896), easily treated, and in which his prolonged headache was alleviated.

Fox (1897) also touted cannabis for headache (p. 307):

> I understand by migraine a periodical nerve storm. . . . For the relief of the paroxysms antipyrin and phenacetin have often been in my experience successful. . . . But I am accustomed to rely

> much upon cannabis indica, having had a pretty large experience of this remedy. The extract, often combined with cascara sagrada [*Rhamnus purshianus* DC Rhamnaceae, a laxative], has controlled many, if not most, cases of migraine. . . . I prefer to use the fresh extract, and have in a good many instances given it to the point of intoxication. This, however, does no permanent harm.

An American 1898 drug handbook stated the following quaint prose under ''Actions and uses'' for cannabis (Lilly 1898, p. 32):

> Not poisonous according to best authorities, though formerly so regarded. Antispasmodic, analgesic, anesthetic, narcotic, aphrodisiac. Specially recommended in spasmodic and painful affections; for preventing rather than arresting migraine; almost a specific in that form of insanity peculiar to women, caused by mental worry or moral shock.

That year, a case report documented symptoms of cannabis overdose in a young woman whose headache was relieved, but who had nonetheless administered a second dose after 4 hours (Roche 1898).

At the turn of the last century, Shoemaker (1899) reported two supportive case studies from Philadelphia. One pertained to a 26 year-old male whose attacks of hemicrania were incapacitating, lasting 48 hours (p. 485):

> Cannabis indica brought him more relief than he had obtained from any other substance. Convinced by experience, he had recourse to this remedy as soon as he felt the slightest promonition of and attack. He would sometimes succeed in aborting a paroxysm and upon other occasions the severity of an attack would be much mitigated.

In the other case, the concomitant occurrence of migraine and dysmenorrhea was successfully treated with cannabis (p. 484), ''In migraine, hemicrania, or sick headache the use of this remedy is often productive of excellent results.''

In *The New American Family Physician* by (Lyman, Jones and Belfield 1899), the authors recommended for headache (p. 340):

> Where there is no evident disturbance of digestion to account for the difficulty, and where the individual is ''nervous,'' the following prescription may be given:

> Extract of guarana, - - - - - - - - - 40 grains
> Extract of cannabis indica, - - - 30 grains
> Citrate of caffeine, - - - - - - - - - 60 grains
>
> Mix, and make 40 pills; take one pill, and repeat the dose after two hours if not relieved.

Contemporaneously, a British pharmacologist extensively studied cannabis (Dixon 1899), recognizing its value as an appetite stimulant, supporting its current indications in the cachexia of cancer chemotherapy and HIV-positive patients. Dixon also lauded smoked cannabis (p. 1356):

> In cases where an immediate effect is desired the drug should be smoked, the fumes being drawn through water. In fits of depression, mental fatigue, nervous headache, and exhaustion a few inhalations produce an almost immediate effect, the sense of depression, headache, feeling of fatigue disappear and the subject is enabled to continue his work, feeling refreshed and soothed. I am further convinced that its results are marvellous in giving staying power and altering the feelings of muscular fatigue which follow hard physical labour. . .
>
> Hemp taken as an inhalation may be place in the same category as coffee, tea, and kola [*Cola acuminata* or *C. nitida* Sterculiaceae, tropical African trees whose nuts contain caffeine]. It is not dangerous and its effects are never alarming, and I have come to regard it in this form as a useful and refreshing stimulant and food accessory, and one whose use does not lead to a habit which grows upon its votary. . .
>
> Like any stimulant or sedative narcotic, hemp may be abused as when taken to produce an intoxicant or deliriant effect, but this abuse is rare and there is reason to believe has been grossly exaggerated. . .
>
> I believe it to be an exceedingly useful therapeutic agent, one not likely to lead to abuse, and producing in proper dosage no untoward after-effects.

The latter comments are pertinent in terms of later allegations of an ‘‘amotivational syndrome’’ attached to people who engage in daily use of cannabis. Apparently, physicians of the age noted no such effect employing hemp preparations in their patients.

In a note added in proof, the editor stated (p. 1357), "Dr. R. B. Wild remarked that cannabis indica–was also of value in certain cases of functional headache."

Lewis (1900) reported on *Cannabis indica* (p. 250), "In migraine, hemicrania, neuralgias, and headache due to eye-strain, it may be used with marked success."

In a contemporary text (Wood and Wood 1900), the authors stated (p. 166), "In full doses in *neuralgic* pains, it certainly often gives relief. . . . As first suggested by Seguin, hemp extract, administered for months continuously in such dosed as will keep just within the limit of distinct physiological effects, is often effective in *migraine."*

Marshall (1905) opined that other medicines had supplanted cannabis for some indications but (p. 451), "It appears, however, to be useful in headache of a dull continuous character. The extract in the form of pills is usually administered."

In 1906, a popular treatise continued to discuss smoking as a mode of medical application (Allbutt and Dixon 1906) (p. 965), "the drug, generally as ganja, may be smoked, when the symptoms come on almost immediately but do not last so long."

It was also noted of Indian hemp (Allman 1911) (p. 765), "In full doses it certainly gives relief in acute neuralgic pains, . . ."

As late as 1915, Sir William Osler, the acknowledged father of modern medicine stated of migraine treatment (Osler and McCrae 1915) (p. 1089), "Cannabis indica is probably the most satisfactory remedy. Seguin recommends a prolonged course of the drug." This statement provided continued support of its use for both acute and prophylactic treatment.

Ratnam (1916) repeated Dixon's quotation in reference to the therapeutic effects of smoked cannabis for headache treatment.

In 1918, *The Dispensatory of the United States of America* stated (Remington et al. 1918, p. 280), "For its analgesic action it is used especially in pains of neuralgic origin, such as *migraine*, but is occasionally of service in other types." This language was retained in the 21st edition in 1926, and the 1937 22nd edition continued to refer to an indication for cannabis in "migrainic headaches."

By this time in the 20th century, cannabis was suffering a political downturn. In 1914, it was dropped from the pharmacopoeia of Ceylon (Sri Lanka), over the vociferous objections of its adherents, such as Ratnam (1920) and others. His points of debate included passionate

defenses of its medical benefits, and poignant political arguments based on multiple facts and figures comparing its benignity to the dangers of other "recreational" drugs. Ultimately, Ratnam addressed a remaining clinical need for cannabis (p. 42):

> "In some cases where there is continued pain in the head lasting for a length of time, Cannabis Indica seems to help and this may be given either in the form of extract or tincture. There is no danger in it. . . . The long continued use of this drug will sometimes relieve these headaches when other things seems to fail." The above authoritative statement was made by Sir T. Lander Brunton, M.D., D.Sc., L.L.D., F.R.S., Physician to St. Bartholomew's Hospital and Lecturer on Pharmacology before the British Medical Association without a dissentient voice.

In the German literature, cannabis use by extract or smoking was held to be an "outstanding agent" (Dinand 1921, p. 71) (translation Schloesser).

Hare (1922) continued to advocated use of cannabis noting (p. 181), "For the relief of *pain*, particularly that depending on nerve disturbance, hemp is very valuable." He went on to state, "In true *migraine* with hemianopsia this treatment is often most effectual in aborting the attack. The prevention of further attack is to be attained by the use of smaller amounts of the cannabis during the intervals . . ." An examination of alternative medications listed in that edition is illuminating: ammonium benzoate, amyl nitrate, bromide of potassium, croton chloral, gelsemium, phenacetin, salicylic acid, and sodium phosphate. Most have passed into obscurity, or are considered ineffective, or even toxic in modern practice.

Dixon (1923) revisited the issue of smoked cannabis, and decried the poor quality of drug available in England. His independent bioassays revealed effects of smoking imported *ganja* and *charas* lasting only one half-hour. Doubtless, many patients and clinicians were lead to believe in the herb's inefficacy by such experiences.

In the years that followed, cannabis came to be perceived as a drug of abuse, smoked by certain minorities in the USA as "marijuana" or "marihuana." In an article provocatively entitled "The Weed of Insanity" the author nevertheless conceded (Bragman 1925, p. 416), "It has some value in the relief of migraine."

The following year, Stevens (1926) remained a convinced user of cannabis for migraine (p. 1115):

> Cannabis indica is sometimes very useful, when a reliable preparation can be secured. Two drops of the fluid extract may be given every half hour until the pain abates or until slight dizziness or mental confusion appears. Even larger doses may be used, if necessary. Morphin should never be employed, except as a last resort.

In a definitive tome of the era (Solis-Cohen and Githens 1928) it was stated (pp. 1704-1705):

> Cannabis is of great service in certain cases of migraine not dependent upon, nor aggravated by, eyestrain. It may be given in dose of 1/4 to 1/2 grain (0.015 to 0.03 Gm.) of the extract, repeated in two hours if sleep has not been produced. According to Mattison, the persevering use of the remedy twice a day for weeks or months, will in many cases, especially in the young, blot out this neurotic taint.

At this time, Walther Straub, Professor of Pharmacology of the University of Munich retained interest in the titration available by the smoking route (Straub 1931, p. 16), ‘‘More time is required for the enjoyment of hashish than for opium, but less than for alcohol. It requires still better dosing, and here the empirical instinct found that the safest dose can be attained by smoking the substance.’’

In a comprehensive review article on headache, Henry Alsop Riley stated (Riley 1932, p. 515), ‘‘Cannabis indica has been much used in the treatment of migraine.’’

Despite its contemporary political downturn in popularity, Fantus (1933) reviewed therapeutic techniques, recommending (p. 879), ‘‘fluid-extract of cannabis,’’ ‘‘One teaspoonful in water every two hours until relieved. (For migraine.)’’

Bastedo (1937) decried the variability of quality of cannabis in his textbook, but noted (p. 460), ‘‘A good preparation of it may allay nervous excitability, as after sexual or alcoholic excesses, may lessen the pain of neuralgia or migraine, and may promote sleep (in the presence of pain).’’

In 1937, marijuana was rendered essentially illegal in the USA

(Baum 1996; Bonnie and Whitebread 1970). Cannabis had become a phytochemical scapegoat for a perceived social problem, and research on its medical uses was substantially curtailed. The American Medical Association vigorously opposed this development (Cary 1937).

Despite this political event, in 1938 Robert Walton published a comprehensive review of cannabis with botanical, historical, chemical and political discussions (Walton 1938). After addressing the issues of its purported abuse, and consequent legislation, he went on to discuss its utility in migraine, citing many of the above sources. He referred to twelve major authorities on its efficacy, and one from a detractor (Beckman 1938) (p. 595), ''The U.S.P. extract of cannabis (better known as Cannabis indica) formerly enjoyed the reputation of being almost specific when used in a pill containing 1/6 to 1/4 grain (0.01-0.015 Gm.), not to be too often repeated, but has latterly fallen into a probably deserved disrepute.''

In 1941, cannabis preparations were dropped from the *United States Pharmacopoeia* (*USP*) and *National Formulary* (*NF*), but the following year, the editor of the *Journal of the American Medical Association* still advocated oral preparations of cannabis in treatment of menstrual (catamenial) migraine (Fishbein 1942) (p. 326):

> In this instance the patient may be given either sodium bromide or fluidextract of cannabis three days before the onset of the menstrual period, continued until three days after the menstrual period.
>
> . . . The dose of the fluidextract of cannabis is five drops three times daily, increased daily until eleven drops, three times daily, are taken. Then the dosage is reduced by one drop daily until five drops are taken three times daily and so on.

As a seeming afterthought, he added, ''Ergotamine tartrate may also be given.'' The latter medicine remains in the migraine armamentarium, some 60 years later, but he considered it inferior to cannabis.

Thus, as demonstrated, cannabis was touted in the mainstream Western medical literature for a full century as a, or the, primary treatment for migraine.

Modern Ethnobotanical Data

Despite political issues in the USA, medical use of cannabis continued elsewhere. In 1947, an ethereal extract of cannabis was employed

for migraine treatment in Argentina (Kabelik, Krejei, and Santavy 1960). Cannabis was recommended as a homeopathic remedy for migraine in 1956 in East Germany (Auster and Schafer 1955).

In Tashkent in the 1930's, cannabis or *nasha* was employed medicinally, despite Soviet prohibition (Benet 1975) (pp. 46-47), ''A mixture of lamb's fat with *nasha* is recommended for brides to use on their wedding night to reduce the pain of defloration. The same mixture works well for headache when rubbed into the skin; it may also be eaten spread on bread.''

Smith (1911) documented its utilization in China, where cannabis remained a useful item in the pharmacopoeia (pp. 90-91), ''Every part of the hemp plant is used in medicine; the dried flowers, the achenia, the seeds, the oil, the leaves, the stalk, the root, and the juice.''

Burkhill (1935) noted continuing usage of *ganja* flowering tops as one ingredient in a pill for headaches in Malaya. Perry and Metzger (1980) referred to ongoing use of cannabis in China to treat migraine, much the same as noted in Thailand (Dhavadee 1987). In other areas of Southeast Asia its use remains popular (Martin 1975, p. 70):

> Everywhere it is considered to be of analgesic value, comparable to the opium derivatives. Moreover, it can be added to any relaxant to reinforce its action. Cooked leaves, which have been dried in the sun, are used in quantities of several grams per bowl of water. This decoction helps especially to combat migraines and stiffness; taken before sleep and before meals, it relaxes the nerves.

A very recent study documents the ethnobotanical uses of cannabis by the Hmong minority in the China-Vietnam border region (Gu and Clarke 1998). The authors described its medical usage (p. 6):

> Some herbal remedies are used by the Hmong, and cannabis seeds, leaves and stalks are used for various indications. Raw seeds are thoroughly chewed and used as a poultice in the forehead for headache relief . . .
>
> Some older Hmong men may rarely smoke cannabis to ''relieve discomfort,'' but they are not daily smokers.

Analgesic effects of cannabis have remained noteworthy in the folk medicine of North Africa (Boulos 1983). As late as 1957, despite

governmental regulation in that country, cannabis drugs retained a role in the indigenous medicine of India (Chopra and Chopra 1957, p. 12), "The concentrated resin exudate–is considered valuable in preventing and curing sick-headaches, neuralgias and migraine . . ."

Nadkarni (1976) observed (p. 203), "The concentrated *resin* exudates–is valuable in preventing and curing sick-headaches, neuralgias, migraine . . ." In a subsequent treatise entitled *Indigenous Drugs of India* (Chopra 1982) the authors stated (p. 91), "Cannabis is used in medicine to relieve pain, to encourage sleep, and to soothe restlessness. There is little definite knowledge of the therapeutic effects produced, but in some persons it appears to produce euphoria and will often relieve migraine headaches."

In discussing the native use of cannabis and opium products by village doctors in India, who provided 80% of the population with their medical care, the author of a report to the United Nations felt a legitimate role for them was still present (Dwarakanath 1965) (p. 19):

> These drugs should be allowed to be used by Ayurvedic and Unani [Arabian tradition] physicians until such time as the benefits of modern medicine are extended to rural areas. Banning their use by the large mass of Ayurvedic and Unani physicians for therapeutic purposes may create a vacuum which may not be easily filled for a long time to come.

Another book about medicinal plants of India stated (Dastur 1962) (p. 67):

> Charas is the resinous exudation that collects on the leaves and flowering tops of plants [equivalent to Arabic *hashish*]; it is the active principle of hemp; it is a valuable narcotic, especially in cases where opium cannot be administered; it is of great value in malarial and periodical headaches, migraine–Charas is usually given in one-sixth to one-fourth grain doses.

In a more recent review of Ayurvedic medicine (Kapoor 1990), the author echoed the above indications but recommended doses of (p. 97), "*ganja* [flowering tops of female cannabis plants]–1-2 gr; *charas*–1/2 gr."

Similarly, in Nepal, cannabis remains useful for headache treatment. According to Drs. Purushottam Shrestha and Narendra Nath

Tiwari (personal communication, July 2000), the *Bhavparaksh Nighantu* (Misra 1988) describes a technique by which flowering tops of cannabis are powdered, hung in muslin above a pot of boiling cow's milk, and then fried in *ghee* (clarified butter). Headache suffers, especially women, take 60-125 mg a day of the treated material.

Dr. Farid Alakbarov reports cannabis use in migraine in Azerbaijan (Alakbarov 2000) (personal communication, June 2000).

Even today in Iran, the indication for cannabis for headache is retained. Zargari (1990, p. 434-438, translation courtesy of H. Akhani and M. O'Yarhossein) notes *Cannabis indica* products "can be used to relieve nervous pains and rheumatism . . ." An alcoholic extract with two other ingredients is also compounded as a "prescription for recovering [from] migraine pains . . ."

Examples are also to be found in the New World. In Colombia the analgesic effects of a cannabis tincture were observed (Partridge 1975, p. 161), "the knowledge that cannabis can be used for treatment of pain is widespread . . ." Rubin et al. documented extensive medical usage of cannabis for a variety of conditions in Jamaica (Rubin 1976; Rubin and Comitas 1972), including headache. Extensive interviews revealed that *ganja* tea was commonly acknowledged to treat headache. Interestingly, among 43 subjects interviewed about their first exposure to smoked cannabis, headache was the only side effect among many suggested symptoms that failed to be claimed. Only one subject noted headache on any subsequent exposure (Lambros Comitas, personal communication, July 2000).

Ultimately, a modern study of chronic use of cannabis has been undertaken in Costa Rica (Carter 1980), detailing medicinal use for asthma, but also (p. 24), "The simple smoking of marijuana is claimed by users to have a number of additional medical benefits. It is said to cure headaches, hangovers, loss of appetite, impotence, depression and general malaise." The adoption of cannabis for headache in cultures remote from its Eurasian origins is particularly noteworthy. Separate citations of identical medicinal claims for a plant for the same indication is widely acknowledged in ethnobotany as strongly supporting clinical efficacy (Russo 1992).

Recent Research on Cannabis and Cannabinoids

In the next two decades, marijuana moved to center stage of Western consciousness, not as a medicinal agent, but rather as a perceived

drug of abuse. Research resumed only slowly, with occasional anecdotal reports by patients of cannabis' benefits on their illnesses.

A popular treatise on marijuana noted medicinal effects (Margolis and Clorfene 1969, p. 26), "You'll also discover that grass is an analgesic, and will reduce pain considerably."

The eminent psychopharmacologist, Solomon Snyder, wrote a popular, but scientifically noteworthy review of cannabis during this era (Snyder 1971, p. 10):

> Migraine headaches can be so incapacitating that, besides easing the acute pain, it is important to attempt to prevent future attacks or at least reduce their frequency and severity. In modern medicine these two tasks are the province of two different types of drugs. Ergot derivatives, such as ergotamine, alleviate acute migraine headaches, while methysergide (Sansert)–which, interestingly, is a close relative of LSD–is used to ward off future headaches. There are indications that cannabis may fulfill both roles.

Snyder examined cannabis' pros and cons as an analgesic (p. 14):

> In one important way, opiates are better than cannabis. They are stronger pain-killers. For the excruciating colicky pain produced by a kidney stone or the crushing chest pain of an acute heart attack, morphine is a blessing. For these conditions, cannabis is much too weak. But its relatively weak pain-relieving action could not possibly account for the neglect of cannabis in modern medicine. For there are many conditions, such as migraine headaches or menstrual cramps, where something as mild as aspirin gives insufficient relief and opiates are too powerful, not to mention their potential for addiction. Cannabis might conceivably fulfill a useful role in such conditions.

President Nixon convened a National Commission on Marihauna and Drug Abuse that recommended decriminalization of cannabis use, and further medical research (United States Commission on Marihuana and Drug Abuse 1972, p. 222):

Therapeutic Uses

> RECOMMENDATION: INCREASED SUPPORT OF STUDIES WHICH EVALUATE THE EFFICACY OF MARIHUANA IN

> THE TREATMENT OF PHYSICAL IMPAIRMENTS AND DISEASE IS RECOMMENDED
>
> Historical references have been noted throughout the literature referring to the use of cannabis products as therapeutically useful agents. Of particular significance for current research with controlled quality, quantity and therapeutic settings, would be investigations into the treatment of glaucoma, migraine, alcoholism and terminal cancer.

The findings of this commission were largely ignored by the administration.

In 1974 began a series of studies that formally examined effects of cannabis on pain. Noyes and Baram (1974) described case studies of five patients who voluntarily employed it to treat their painful conditions. Three of these had chronic headaches. Case 2 pertained to a graduate student who found smoked cannabis to be almost as effective at treating acute migraine as an ergotamine/phenobarbital preparation. The cannabis also seemed to reduce attack frequency (unlike his usual combination that can produce analgesic rebound).

In Case 3, a housewife had successfully treated headache with cannabis smoking for a year with "immediate and lasting relief" she considered superior to aspirin (p. 533). Case 5 pertained to another graduate student, who over two years found that smoked cannabis relieved headaches about 70% of the time (comparable to the best standard pharmaceuticals at present).

A similarly composed research group compared the analgesic effect of THC was compared to codeine (Noyes et al. 1975). In short, 10 mg of oral THC reduced subjective pain burdens by similar decrements to 60 mg of codeine, as did 20 mg of THC vs. 120 mg of codeine. This supports the observations of Hobart Hare almost one century earlier. Subjects in this experiment tolerated 10 mg of THC well, but 20 mg produced sedation and psychic disturbances in some relatively elderly cannabis-naïve subjects.

Another government-sponsored commission evaluated *Marijuana and Health* (Institute of Medicine 1982), their findings echoing those of prior studies (p. 150):

> Cannabis and its derivatives have shown promise in the treatment of a variety of disorders. The evidence is most impressive in

> glaucoma, . . . in asthma, . . . and in the nausea and vomiting of cancer chemotherapy. . . . Smaller trials have suggested cannabis might also be useful in seizures, spasticity, and other nervous system disorders.
>
> . . . The committee believes that the therapeutic potential of cannabis and its derivatives and synthetic analogues warrants further research. . .

Greater governmental cooperation in the development of research protocols in humans was suggested, but the US government printed only 300 copies of the report (Mathre 1997).

In "Health Aspects of Cannabis," Hollister (1986) addressed possible medical indications, but his direct experience with cannabis use in migraine was not broad (p. 16):

> *Migraine:* This indication has not been studied systematically in recent years, although it has a long history. In one patient I treated, the mental effects sought socially caused the patient to abandon treatment. Innumerable successful treatments for migraine have been reported at one time or another.

Mechoulam (1986) published *Cannabinoids as Therapeutic Agents*, wherein the author stated and then inquired (p. 16):

> For the medical scientist use of cannabis as a therapeutic agent in the past may serve as a clue to future drug development. Many of the therapeutic properties of cannabis have been verified with pure natural or synthetic cannabinoids. In several fields, however, no modern work exists. The most blatant examples are the antihelmintic, anti-migraine, and the oxytocic effects. Are we missing something?

The following year, another article dealt with the headache issue more directly (el-Mallakh 1987). Entitled "Marijuana and Migraine," three cases were discussed in which abrupt cessation of frequent, prolonged, daily marijuana smoking was followed by recurrent migraine attacks. One patient noted subsequent remission of headaches with a return to episodic cannabis use, while the two others employed "conventional drugs" successfully. THC's peripheral vasoconstrictive actions in rats, or its action to minimize serotonin release from the

platelets of human migraineurs (Volfe, Dvilansky, and Nathan 1985), were felt to be possible explanations of its therapeutic effects.

The book *Marihuana: The forbidden medicine* (Grinspoon and Bakalar 1993) included an entire section on migraine. One clinical vignette documented the medical odyssey of a migraineur through failures with standard pharmaceuticals. Over a period of 18 years, she found that a little smoked cannabis and rest for 30 minutes allowed her to return to work. Both of her daughters subsequently treated their attacks in similar fashion, but her mother resisted due to its illegality.

The *American Journal of Public Health* issued a particularly strong plea for access to therapeutic cannabis (Anonymous 1996, p. 441), acknowledging its role in ''decreasing the suffering from chronic pain.''

Recently, the debate on the subject of ''medical marijuana'' has extended to the World Wide Web. One posted document (Mikuriya 1997) is ''Chronic Migraine Headache: five cases successfully treated with Marinol and/or illicit cannabis.'' Two patients were prescribed dronabinol (synthetic THC) for their headaches with improvement, but some degree of side effects, or difficulties with overwhelming cost. Both switched to marijuana, with an improved clinical response and decreasing frequency and severity of attacks. Another family of three women smoked marijuana acutely with good success in aborting headache, often in the prodromal phase.

A second Web document entitled ''Cannabis Medicinal Uses at a 'Buyers' Club' '' (Mikuriya 1995) examined the indications that prompted patients to seek out this treatment. Of the 57 people interviewed, eleven identified migraine as the culprit condition that prompted their decision to self-medicate with cannabis.

In another Internet document, the author (Terwur 1997) described regular successful treatment of migraine attacks and associated symptoms with cannabis resin in a fashion that did not produce inebriation.

Petro (1997) offered a published account on cannabis use in migraine in which a 34-year-old woman found superior relief and prophylaxis with cannabis as compared to beta-blockers, opiates or ergots. Frequency dropped from 3-4 attacks to one per month.

A British group recently reviewed their clinical experience employing the synthetic cannabinoid, nabilone, as an analgesic, including neuropathic pain (Notcutt, Price, and Chapman 1997). Nabilone is employed orally, but causes drowsiness and dysphoria. Several pa-

tients cited better pain relief with smoked cannabis, with fewer side effects. Nabilone was also estimated to cost 10 times as much as street cannabis. The authors stated (Notcutt, Price, and Chapman 1997, p. 554), "Cannabis can be cloned and grown to yield a cocktail of cannabinoids of known and repeatable concentrations. The illogicalities are evident." They closed by observing (p. 555):

> we must not lose sight of the fact that there are a large number of patients with chronic pain who might benefit from this group of drugs [cannabinoids]. Currently their options for analgesia are limited or non-existent. This is particularly poignant when one considers the history and safety of cannabis.

Hollister (2000) recently reviewed indications for cannabis. On the one hand, he states (p. 5), "for exploratory purposes, any patient with pain unrelieved by conventional analgesics should have access to smoked marijuana if they so desire." A few paragraphs later, however, he decries, "New drugs for migraine are aimed at pathogenetic mechanisms rather than symptomatic treatment. Virtually no literature exists that support this use of marijuana."

Despite this view, the *PDR for Herbal Medicines* (Medical Economics Company 2000) lists *Cannabis sativa* under its Indications Index for migraine headache (p. I-103), and states (p. 501), "Current literature on phytotherapeutic drugs cite as indications for Indian hemp: . . . migraine; . . ."

ALTERNATIVE DELIVERY SYSTEMS

Alternative smoke delivery systems have been investigated for cannabis (Gieringer 1996; Gieringer 1996). Reportedly, vaporization of marijuana makes it possible to deliver even high doses of THC to the lungs of a prospective patient far below the flash point of the cannabis leaf, thus reducing smoke, tar and other possible carcinogens. However, the standard marijuana joint remained about as effective as any examined smoking device, including those employing water filtration, in providing a favorable ratio of THC to tar and other undesirable by-products. A standardized smoking procedure for use of cannabis in medical research has been described (Foltin, Fischman, and Byrne 1988).

Suppository preparations of cannabis have been used to advantage in the past, and may be an acceptable alternative route of administration for the migraineur, although the advantage of dose titration would be lost. GW Pharmaceuticals in the UK is researching nebulized and sublingual preparation with whole cannabis extracts.

THE DISCOVERY OF ENDOGENOUS CANNABINOIDS AND BIOCHEMICAL MECHANISMS OF CANNABINOIDS

Recently, scientists have provided elucidation of the mechanisms of action of cannabis and THC with the discovery of an endogenous cannabinoid brain receptor, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda*, or "bliss" (Barinaga 1992; Devane et al. 1992; Marx 1990; Matsuda et al. 1990). Anandamide has an inhibitory effect on cyclic AMP mediated through G-protein coupling in target cells, which, though widespread in the brain, cluster in nociceptive areas (Herkenham 1993). Preliminary tests of its pharmacological action and behavioral activity support similarity to THC (Fride and Mechoulam 1993). Pertwee (1997) has examined the pharmacology of cannabinoid receptors in detail.

Additional research has elucidated mechanisms of therapeutic action of the cannabinoids pertinent to migraine, which are examined system by system.

CANNABINOIDS AND SEROTONERGIC SYSTEMS

Serotonergic mechanisms have long been implicated in migraine pathogenesis and treatment. This mechanism has been specifically targeted in the development of the triptan drugs (Humphrey, Feniuk, and Perren 1990). THC reduces serotonin release from the platelets of human migraineurs (Volfe, Dvilansky, and Nathan 1985). Cannabis has also been reviewed in the French literature (Spadone 1991). Among other points, the author indicated (p. 21):

> As to serotonin, the synthesis of 5-HT is stimulated by THC (possibly by intermediary augmentation of corticosteroids) as well as brain 5-HT content. Synaptosomal uptake seems inhibited, while release is favored. [translation EBR]

Anandamide and other cannabinoid agonists inhibit rat serotonin type 3 ($5\text{-}HT_3$) receptors (Fan 1995). This receptor acts as a mediator of emetic and pain responses. The dearth of cannabinoid receptors in the area postrema (Herkenham et al. 1990; Fride and Mechoulam 1996) coupled with the clinical effectiveness of cannabinoids as anti-emetics (Abrahamov and Mechoulam 1995), support such an alternative mechanism.

Recently, Boger demonstrated an 89% relative potentiation of the $5\text{-}HT_{1A}$ receptor and a 36% inhibition of the $5\text{-}HT_{2A}$ receptor responses by anandamide (Boger, Patterson, and Jin 1998). 2-AG or arachidonylglycerol (another endocannabinoid) inhibited $5\text{-}HT_{2A}$ by 28%. Similar effects by THC are likely. These observations support efficacy for cannabinoids in acute symptomatic migraine treatment (agonistic activity at $5\text{-}HT_{1A}$ or $5\text{-}HT_{1D}$) and in prophylactic treatment of chronic headache (antagonistic activity at $5\text{-}HT_{2A}$) (Peroutka 1990a and 1990b).

In a similar vein, Kimura et al. (1998) showed that high concentrations of anandamide decreased serotonin and ketanserin binding (the latter being a $5\text{-}HT_{2A}$ antagonist). Additionally, 11-OH-delta-8-THC and 11-oxo-delta-8-THC metabolites of cannabis modified serotonin receptor binding.

Ultimately, the author and colleagues have recently demonstrated pertinent serotonin receptor activity of the essential oil of cannabis (Russo et al. 2000). Dilutions of these terpenoid components of up to 20,000 in buffer produced displacements of at least 50% of ^{3}H-ketanserin from the cloned $5\text{-}HT_{2A}$ receptor, while the same material displaced ^{3}H-8-OH-DPAT from the $5\text{-}HT_{1A}$ receptor at least 50% in dilutions up to 400. This activity provides important evidence for putative synergistic activity of cannabis essential oil components with THC in the preventive and symptomatic treatment of migraine.

DOPAMINERGIC SYSTEMS

The importance of dopaminergic mechanisms in migraine treatment has received recent emphasis (Peroutka 1997). Dopamine blocking drugs such as chlorpromazine and haloperidol can be very effective stand-alone or adjunctive agents in migraine, but are significantly sedating.

Ferri et al. (1986) were able to demonstrate that 6-hydroxydopa-

mine, which causes degeneration of catecholamine terminals, was able to block THC antinociception. Stefano and his team showed that anandamide stimulates nitric oxide formation in lower animals through inhibition of presynaptic dopamine release (Stefano et al. 1997). They stated (p. 63), "cannabinoids and their endogenous effectors play a prominent role in the regulation of catecholamine release in invertebrates . . ." Many cannabinoid mechanisms demonstrate teleological preservation, and similar effects in higher mammals may well be operative. In a recent review (Mechoulam, Fride, and Di Marzo 1998) (p. 12), a number of studies were cited as demonstrating that cannabimimetic drugs cause "inhibition of the dopaminergic nigrostriatal system."

Müller-Vahl and her colleagues cited previous work (Mailleux and Vanderhaeghen 1992) in their examination of cannabinoid effects on the dopaminergic system (Müller-Vahl et al. 1998, p. 504), "cannabinoid receptors were found to be co-localized both with dopamine D_1 receptors on striatonigral dynorphin/substance-P-containing neurones and with dopamine D_2 receptors on striatopallidal enkephalinergic neurones." This and subsequent work by her group (Müller-Vahl et al. 1999) demonstrates that cannabis is able to induce a considerable decrement in the movement disorder of patients with Tourette syndrome. This suggests a possible dopamine blocking effect of THC, which may be clinically relevant without significant sedation, but whose mechanism remains to be elucidated. Similar effects of THC on the dopaminergic system may be equally pertinent to migraine treatment.

Leweke et al. (1999) demonstrated elevated levels of anandamide and palmitylethanolamide (PEA) in schizophrenic patients, stating (p. 1666), "anandamide may act as a local modulatory signal to offset dopamine-induced psychomotor activation." Given the tendency of schizophrenics to "self-medicate" with cannabis, there is support for their statement that their findings, "may reflect a homeostatic adaptation of the endogenous cannabinoid system to neurotransmitter imbalances that involve dopamine." Conjecturally, THC may similarly modulate dopaminergic imbalances in migraine, and deserves study.

INFLAMMATORY MECHANISMS

Anti-inflammatory claims for cannabis date back to the Sumerians binding the head with the herb (Thompson 1949). Modern authors

(Burstein 1992; Evans, Formukong, and Evans 1987; Formukong, Evans, and Evans 1988, 1989) have examined the relationship between cannabinoids and inflammation. It is well known that anti-inflammatory drugs may ameliorate migraine, perhaps through effects on the "sterile inflammation" of that disorder, as well as effects on the arachidonate cascade. McPartland (2000) provides an excellent summary and analysis (McPartland 2000).

Burstein et al. (1973) demonstrated that THC and other cannabinoids could inhibit prostaglandin E-2 synthesis, and that the aromatic moiety seemed to be the critical portion. In 1979, it was experimentally demonstrated that smoked cannabis reduced platelet aggregation (Schaefer et al. 1979).

Cannabichromene is often the second most abundant cannabinoid in marijuana after THC (Turner and ElSohly 1981). CBC proved superior in its anti-inflammatory capabilities to phenylbutazone. The authors stated (p. 283S), "it is obvious that the THC content of marihuana cannot be used to adequately describe the pharmacologic activity of the drug."

Evans (1991) further analyzed structure-activity relationships of cannabinoids, stating (p. S65), "Experiments involving oral administration of THC suggested that THC was 20 times more potent than aspirin and twice as potent as hydrocortisone." Also observed was the action of CBD as a dual cyclooxygenase and lipoxygenase inhibitor in various assays. Hampson et al. (1995) were able to demonstrate that anandamide and metabolites are substrates for brain lipoxygenase.

Although some authors have reported THC as an inhibitor of tumor necrosis factor (TNF) production, Klein et al. (1998) noted that levels of the latter might rise or fall depending on the cells and culture system selected.

In a recent review (Fimiani et al. 1999), the authors analyze the respective roles of opiate, cannabinoid and eicosanoid signaling through a common nitric oxide coupling. They note (p. 27), "Delta-9-THC blocks the conversion of arachidonic acid into all metabolites derived by cyclooxygenase activity, whereas it stimulates lipoxygenase, resulting in an increase in lipoxygenase products." The COX inhibition of THC may in fact be selective for the COX-2 isozyme, as more fully discussed by McPartland (2000). Clinically, no increased incidence of gastric ulceration in chronic cannabis users has been observed (Stefanis, Dornbush, and Fink 1977; Rubin and Comitas

1975; New York (City), Mayor's Committee on Marihuana, Wallace, and Cunningham 1973), thus supporting its likely selectivity for COX-2. One essential oil sesquiterpene component of cannabis, caryophyllene, has a gastric cytoprotective effect (Tambe et al. 1996).

The above authors (Fimiani et al. 1999) also noted the morphine-cannabinoid system modulates the eicosanoid cascade and its pro-inflammatory cytokine activity through induction of nitric oxide synthesis, averting damaging effects on tissues. They summarized (p. 30), "Thus, we can surmise cannabinoid-morphine systems are down-regulators of inflammatory processes in an attempt to restore homeostasis."

Additionally, cannabis seed has likely dietary benefits as an anti-inflammatory agent. It is a rich source of linolenic acid, which promotes formation of anti-inflammatory metabolites, as well as providing significant amounts of gamma-linolenic acid, inhibiting the formation of pro-inflammatory products from arachidonate (Conrad 1997; Wirtshafter 1997; Russo 2000).

Flavonoid components of cannabis may potentiate anti-inflammatory activity. Cannflavin A and B inhibited prostaglandin E-2 production in human rheumatoid synovial cells 30 times more potently than aspirin (Barrett, Scutt, and Evans 1986). Apigenin, a flavonoid common to cannabis and German chamomile (*Matricaria recutita* L. Asteraceae), had important anti-inflammatory actions on interleukin, TNF, carrageenan-induced edema and by inhibition of up-regulation of cytokine-induced genes (Gerritsen et al. 1995). Quercetin, another flavonoid in cannabis, serves as an antioxidant, and inhibits hydrogen peroxide-mediated NF-kappaB activity (Musonda and Chipman 1998).

Finally, various terpenoid essential oil components of cannabis demonstrate anti-inflammatory effects at physiologically appropriate levels (McPartland and Mediavilla 2001). Burstein et al. (1975) have examined the essential oil fraction of cannabis, demonstrating eugenol as potent in prostaglandin inhibition. Alpha-pinene and caryophyllene have proven to demonstrate anti-inflammatory activity in the rat hind-paw edema model from carrageenan or by PGE-1 (Martin et al. 1993).

CANNABINOID INTERACTIONS WITH OPIATES AND ENDOGENOUS OPIOIDS

In "Cellular Effects of Cannabinoids" (Martin 1986), the author reported that naloxone did not block the analgesic properties of these substances, supporting a non-opioid mechanism.

THC experimentally increases beta-endorphin levels (Wiegant, Sweep, and Nir 1987). Depletion of endorphins has been measured in the CSF of migraineurs during attacks (Fettes et al. 1985), and may contribute to hyperalgesia and photophobia. Early exposure to THC in rat pups boosted adult levels of beta-endorphins in specific brain areas, while also raising substance P (Kumar et al. 1990). The pertinence to human patients is unclear. Mailleux and Vanderhaeghen (1994) have also demonstrated that THC regulates substance P and enkephalin mRNA levels in the basal ganglia. Manzanares et al. (1998) have shown THC is able to promote increases in beta-endorphin in rats.

Meng and his group (1998) demonstrated that THC is involved in an analgesic brainstem circuit in the rostral ventromedial medulla that interacts with opiate pathways. They observed (p. 382), ''the release of endogenous opioids in the RVM mediates both the inhibition of 'on' cells and the antinociception seen after activation of neurons in the midbrain periaqueductal grey.''

Cichewicz and her group (1999) have suggested an opiate sparing effect of THC might be employed clinically in pain patients, echoing claims of the 19th century pioneers of Indian hemp.

Many analgesic effects of cannabinoids cannot be reproduced by opiates, however, particularly in cases of neuropathic pain (Hamann and di Vadi 1999). Especially in migraine, opiates may aggravate the condition, or even promote its appearance *de novo* (Nicolodi 1998). Therapeutic doses of morphine were unable to relieve migraine attack and increased hyperalgesia in migraineurs when administered in headache-free intervals. Additionally, 65% of chronic opiate users developed migraine during or subsequent to their addiction.

Meng's results are discussed above (Meng et al. 1998). In a recent publication Manzanares et al. (1999), cited that chronic cannabinoid administration could similarly promote hypothalamic production of beta-endorphin. This effect may be important with respect to autonomic and chronometric effects of migraine.

MIGRAINE, CANNABINOIDS, AND THE PERIAQUEDUCTAL GRAY

In 1996, researchers demonstrated antinociceptive effects of delta-9-THC and other cannabinoids in the periaqueductal gray matter in

rats (Lichtman, Cook, and Martin 1996). The PAG is a putative migraine generator area (Goadsby and Gundlach 1991; Raskin 1988), and is integral to ascending and descending pain pathways, fear and anxiety (Behbehani 1995).

Weiller et al. (1995) examined migraineurs during attacks with positron emission tomography (PET), demonstrating various sites of regional blood flow increase. Those increases persisted in brainstem areas, including the PAG, after successful treatment of the attacks with sumatriptan. The authors posited migraine to reflect an imbalance in activity of brainstem centers mediating vascular tone and antinociception. Similarly, Castro et al. (1997) demonstrated a differential tritiated sumatriptan binding in human PAG, again supporting the crucial nature of that locus in migraine pathophysiology.

Manzanares et al. (1998) suggested that cannabinoid-mediated antinociception in the PAG is produced by activation of endogenous opioids. This is further supported by the fact that subchronic THC administration elevates proenkephalin gene expression in the PAG.

A very recent analysis (Walker et al. 1999), has demonstrated that electrical stimulation of PAG in the rat stimulated anandamide release and CB_1 receptor-mediated analgesia. The system was tonically active, and cannabinoid antagonists produced hyperalgesia. The authors posited that this cannabinoid modulated pain system would support the prospect of approaches with cannabinoids to opiate-resistant syndromes.

NMDA, GLUTAMATE AND MIGRAINE

A trigeminovascular system has long been implicated as subserving pain, inflammatory and vascular effects of migraine. An important neurochemical link of the NMDA/glutamate system to trigeminovascular nociception in migraine has been reviewed in detail (Storer and Goadsby 1999). In essence, painful stimuli in the head produce transmission in the trigeminocervical complex through both NMDA and non-NMDA-mediated mechanisms. One of the observed mechanisms of the triptan drugs in migraine is their ability to block glutamate release and trigeminocervical transmission through modulation of 5-HT_1 receptor subtypes. The authors called for newer agents that would affect this system without vascular side effects of the triptans.

Shen et al. (1996) elucidated basic mechanism of cannabinoids in

glutamatergic systems. Through G-protein coupling, cannabinoid receptors inhibit voltage-gated calcium channels, and activate potassium channels to produce presynaptic inhibition of glutamate release. This effect was noted with endogenous and synthetic cannabinoid receptor agonists, and was felt to be key to their analgesic responses. ''Psychotomimetic'' or rather, dissociative side effects of strongly active agents on the NMDA system (e.g., phencyclidine, ketamine) were noted, while (p. 4333), ''better tolerated drugs appear to be less efficacious inhibitors of glutamate activation, but retain neuroprotective efficacy, consistent with reduction, but not abolition, of glutamate receptor activation.'' Natural cannabinoids fit this profile, as demonstrated in a subsequent study (Shen and Thayer 1999), wherein THC served as a partial agonist acting presynaptically via CB_1 to modulate glutamatergic transmission through a reduction without blockade.

Similarly, Hampson and colleagues demonstrated a 30-40% reduction in delta-calcium-NMDA responses by THC (Hampson, Bornheim et al. 1998), which was eliminated by a cannabinoid antagonist. This group has subsequently provided elegant demonstration of the ability of the THC and cannabidiol components of cannabis to act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA and kainate receptors (Hampson, Grimaldi et al. 1998). These effects seemed to occur independently of cannabinoid receptors, and support presumptive benefit in cerebral ischemia, as observed in migraine infarction. The natural cannabinoids were more potent in their anti-oxidant effects than either alphatocopherol or ascorbic acid.

Italian researchers Nicolodi and Sicuteri (1995) have recently elucidated the role of NMDA antagonists in eliminating hyperalgesia in migraine and possibly other conditions in a series of articles. They demonstrated that ketamine was able to ameliorate migraine both acutely and prophylactically through NMDA blockade. A ''secondary hyperalgesia'' in these patients, manifested by an increased response to noxious stimuli in areas adjacent to the pain was also diminished. They suggested NMDA blockade as a remedy for chronic daily headache (Nicolodi, Del Bianco, and Sicuteri 1997), and related mechanisms of pain in defects of serotonergic analgesia in fibromyalgia (Nicolodi, Volpe, and Sicuteri 1998), which is frequently comorbid. In a most recent study (Nicolodi and Sicuteri 1998), they elucidate mechanisms by which a genetic predisposition (''tertiary hyperalgesia'')

may lead to a "chronicization" of migraine through NMDA stimulation. Gabapentin and ketamine were suggested as tools to block this system and provide amelioration. Given the above observations and relationships, it is logical that prolonged use of THC prophylactically may exert similar benefits, as was espoused in cures of chronic daily headache claimed in the 19th century with regular cannabis usage (Mackenzie 1887).

This concept is bolstered by examination of another series of articles by Richardson and her group. One study examined peripheral mechanisms (Richardson, Kilo, and Hargreaves 1998), wherein cannabinoids acted on CB_1 to reduce hyperalgesia and inflammation via inhibition of neurosecretion of calcitonin gene-related peptide (CGRP) in capsaicin activated nerve terminals. This is akin to mechanisms of "sterile inflammation" observed centrally in migraine where CGRP is felt to be an important mediator. At the spinal level, her group noted an antihyperalgesic effect of cannabinoids (Richardson, Aanonsen, and Hargreaves 1998a), mediated by CB_1. Additionally, experimental cannabinoid receptor blockade induced a glutamate-dependent hyperalgesia, suggesting a tonic activity of cannabinoids in averting such a development. Once more, an inhibition of CGRP release was noted with anandamide. On this basis, they suggested the clinical of cannabinoids in disorders (p. 152) "characterized by primary afferent barrage." Inasmuch as an increased potency of cannabinoids was observed in hyperalgesia (p. 152), "may mean that there are dosages of cannabinoids that would be effective as antihyperalgesic agents but subthreshold for the untoward psychomimetic effects." This is reminiscent of Dixon's patients, able to return to work after treating their headaches with a few inhalations of cannabis (Dixon 1899).

Elaborating on these themes, Richardson noted that a decrease in lumbar cannabinoid receptor numbers correlated with hyperalgesia (Richardson, Aanonsen, and Hargreaves 1998b), and could provide an etiology for certain chronic pain states, especially those unresponsive to opiate treatments, stating (p. 456), "Accordingly, drugs that activate cannabinoid receptors or gene therapy directed at increasing activity of the cannabinoid system may have therapeutic use in treating certain types of chronic pain."

An even more recent study (Li et al. 1999) supports these contentions. The synthetic cannabinoid agonist, WIN 55,212-2 was employed

to block capsaicin-induced hyperalgesia in rat paws much as has been observed for THC in formalin treatment paradigms. The authors stated (p. 30), "These studies support the notion that cannabinoids can block hyperalgesia at doses which do not produce analgesia or affect motor function." They continued (p. 31), "low doses of cannabinoids may represent a novel therapeutic approach for alleviating hyperalgesia–without the unwanted side effects typically associated with these compounds."

Ultimately, Ko and Woods (1999) examined local THC administration and its activity on capsaicin-induced pain in rhesus monkeys. Once more, THC effectively reduced pain, which was blocked by a CB_1 antagonist. THC was effective by injection, at a dose that produced no behavioral change or sedation. The authors observed (p. 322), "Cannabinoid agonists may be effective treatments for nausea associated with chemotherapy, pain, migraine and epilepsy." Critics may point out that the above studies examine peripheral and spinal mechanisms, but are not applicable to supraspinal systems. This seems unlikely. Maneuf et al. (1996) were able to show a tonic activation of the cannabinoid system serving to reduce GABA uptake in the globus pallidus.

The above studies, taken ensemble, provide intriguing evidence that cannabinoid systems may prove to integral to nociceptive pathways in migraine pathogenesis.

SYNERGISM AND THE ENTOURAGE EFFECT

Another potent endogenous cannabinoid with analgesic effects has recently been described (Calignano et al. 1998). Palmitylethanolamide (PEA) is released with from a phospholipid in conjunction with anandamide. The two compounds achieve a 100-fold synergism on CB_1 type peripheral receptors in cutaneous tissues. It has also been shown that endogenous cannabinoids and their inactive metabolites combine to boost physiological responses (the "entourage effect") (Mechoulam and Ben-Shabat 1999). Given the likely contributions of cannabis flavonoids and essential oils to therapeutic effects on mood, inflammation and pain reviewed in (McPartland and Pruitt 1999), one can easily see support for Dr. Mechoulam's quotation (Mechoulam and Ben-Shabat 1999, p. 136), "This type of synergism may play a role in the widely held (but not experimentally based) view that in

some cases plants are better drugs than the natural products isolated from them.''

ONTOLOGICAL CONJECTURE ON THE CANNABINOIDS IN MIGRAINE

Migraine is relatively uncommon before age 10, and very much so before age 5. When present, it may be manifested as ''acephalic migraine,'' or migraine without pain, or as a number of other *formes frustes* such as cyclic vomiting, abdominal pain, or paroxysmal vertigo. The reason for this developmental quirk has never been elucidated.

A detailed developmental mapping of cannabinoid receptor binding in humans has been performed (Glass, Dragunow, and Faull 1997), and may shed light on this issue. Cannabinoid binding is low in the brainstem except for the substantia nigra, spinal trigeminal and tractus solitarius nuclei and the periventricular gray matter, demonstrating an interesting homology with sumatriptan binding in the human brain (Castro et al. 1997). In the adult, midbrain central gray binding of tritiated CP55940 was 21 ± 12 femtomoles/mg of tissue, whereas, in the neonate, the value was 157 ± 11, some 7.5 times greater (Glass, Dragunow, and Faull 1997). Similar increased density of cannabinoid binding is seen in other areas. A decremental decline in cannabinoid binding was observed developmentally.

Given the reported role of the PAG in pain modulation and migraine, it is interesting to conjecture that this decline in its cannabinoid binding allows the subsequent development of migraine pain in the older child or adult. The emesis and abdominal pain of migraine appear early in its ontogeny, but it is clear from previous study that this mechanism is not mediated by cannabinoid receptors.

What of other phenomena of the young? Could it be that the eidetic images, childlike wonder and ready laughter of youth are a manifestation of their greater expression of cannabinoid function? As adults are we consigned to suffer the pain, and lose the intensity of image and imagination? This conjecture is surely worth considering.

VALUE AND PLACE OF CANNABIS IN MIGRAINE TREATMENT

The information reviewed above indicates that cannabis has a long established history of efficacy in migraine treatment. Clinical use of

the herb and its extracts for headache has waxed and waned for 1200 years, or perhaps much longer, in a sort of *cannabis interruptus*.

It is only contemporaneously that supportive biochemical and pharmacological evidence for the indication is demonstrable. Cannabis' unique ability to modulate various serotonergic receptor subtypes, inhibit glutamatergic-mediated toxicities, simultaneously provide anti-inflammatory activity and provide acute symptomatic and chronic preventive relief make it unique among available treatments for this disorder.

This author's personal experience in communicating with several hundred migraineurs who have employed cannabis is that 80% have noted improvement, often with complete symptomatic relief. That this has occurred without any quality control of the herb whatsoever is most compelling. Many report the ability to titrate their dosage through smoking so that they achieve relief without cognitive or motor impairment. The latter is not the case with oral THC (''dronabinol'' or Marinol®), whose slow and variable gastrointestinal absorption and conversion to more intoxicating metabolites (11-hydroxy-delta-9-THC) have made it a poorer choice for most migraineurs.

Reports of surveys of undertaken by Dr. Tod Mikuriya on 2480 patients served by the Oakland Cannabis Buyers' Club indicate that 127 or 5% sought cannabis for primary treatment of chronic migraines (Gieringer 2001).

CANNABIS, AND THE IDEAL DRUG FOR MIGRAINE

Some years ago, this author mused on the pharmacological attributes of an ''ideal drug'' for headache treatment (Russo 1992). Based on contemporary knowledge, these included: stimulatory activity on 5-HT_1 receptors for acute relief, antagonistic activity on 5-HT_2 receptors for prophylactic benefit, antagonism of 5-HT_3 receptors for anti-emesis, boosting of depleted endorphin levels, inhibition of substance P, freedom from gastrointestinal upset, and reasonable cost. Nowadays, we might add inhibition of NMDA receptor activity and CGRP release. It seemed wise to consider that no single agent that met these requirements existed, or could even be conceived. Currently, that judgment requires revision. Cannabis, particularly considered as an admixture of THC, other cannabinoids, flavonoids and essential oils,

seems to fulfill all of these criteria. That proof is offered historically, with anecdotal case studies, and with examination of its biochemical basis. Now all that is required in clinical correlation in modern controlled conditions.

FINAL THOUGHTS

Migraine remains a serious public health issue despite the recent development of 5-HT_{1D}-agonist medications. In the USA, an estimated 23 million Americans suffer severe migraine. Of those, 25% have four or more episodes per month, and 35% have one to three severe headaches each month (Stewart et al. 1992). An estimated 14% of females, and 8% of males miss some part a day of work or school each month due to headaches (Linet et al. 1989). Migraine has been estimated to account for an economic impact of $1.2 to $17.2 billion annually in the USA in terms of lost productivity (Lipton and Stewart 1993).

Although sumatriptan has effected an admirable advance in treating acute migraine, problems remain. While rapidly active subcutaneously, its oral absorption is relatively slow, and absorption of any agent by this route may be notably impaired or impossible in the migraineur. One may inadvertently treat the headache attack too early: sumatriptan and its analogues are ineffective when administered in the "aura phase" of classic migraine (Bates et al. 1994; Ferrari and Saxena 1995). Despite its status as the current most effective agent in acute migraine treatment, injected sumatriptan (Imitrex®) has been ineffective in up to 30% of patients, or has produced undesirable side effects for up to 66% (Mathew 1997). Headache recurrence after triptans remains a common clinical pitfall. Unfortunately, repetitive dosing, and development of agents with longer half-lives does not totally solve the problem (Ferrari and Saxena, 1993, 1995). It is a curious feature of sumatriptan that it is said to pass the blood-brain barrier poorly. Some researchers posit that the condition itself results in easier passage of the molecule. Newer agents with improved central nervous system penetration have been synthesized, but have not notably improved efficacy. Some may result in more frequent chest and throat tightness, numbness, tingling, anxiety, and other side effects (Ferrari and Saxena 1993, 1995). Most importantly the triptan class of medica-

tions does not reduce the frequency of migraine attacks. The older drug dihydroergotamine, has some prophylactic benefit but is best administered intravenously, and is not well tolerated by some. Thus, the triptans, however impressive, may represent a therapeutic dead end. Considering these shortcomings, alternative treatment agents remain an important priority.

Based on the above review, it is convincingly the case that "medical marijuana" deserves formal scientific scrutiny for migraine treatment. Such clinical trials may reveal whether cannabis fulfills current criteria as a safe and effective treatment for migraine. Smoked cannabis would be preferable to butorphanol nasal spray (Stadol-NS®), which has remained an unscheduled drug approved in the USA for migraine treatment notwithstanding its addictive potential and attendant morbidity and mortality (Fisher and Glass 1997).

Although evidence suggests that delta-9-THC is primarily responsible for clinical benefits of cannabis smoking in migraine, investigation of the effects of different cannabis strains rich in tetrahydrocannabivarin (THCV), delta-8-THC, or certain flavonoids and monoterpenes may be clinically fruitful. Use of high potency material for smoking, or alternative delivery systems may provide improved cost-benefit ratios. Solving the above issues may render cannabis or future synthetic cannabinoids well suited to migraine treatment. Given the multiple mechanisms by which cannabis affects migraine pathophysiology, it may come to pass that the disorder is eventually recognized as an endocannabinoid deficiency disease, or a disorder of cannabinoid regulation.

In closing, a unique dance of medical science and politics is occurring that will soon decide whether herbal cannabis (a derivative, or synthetic analogue) will rise like the legendary phoenix to resume an ancient role as a remedy for migraine and neuropathic pain.

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Marijuana and Music: A Speculative Exploration

Peter Webster

ABSTRACT. The extra-therapeutic uses of cannabis and other age-old psychoactive plants are currently ignored or dismissed not only by the usual suspects (moral entrepreneurs, political, religious leaders and other self-proclaimed do-gooders), but also by the great majority of the academic community. Those wishing to experiment with such substances often do so at no small risk to reputation or freedom. Thus, potentially important research has been banished from mainstream science to be accomplished only unofficially, often anonymously, and seldom given recognition when merited. As an example of such unofficial, unpublished, and underground research, the author presents a speculative exploration on the cannabis-produced altered state of consciousness and its relation to the appreciation and production of music. Hypotheses will be offered for consideration concerning the neurocognitive changes brought about by cannabis and how these may produce various useful effects. Aspects of the development of jazz music in the 20th century are presented which provide support for the hypotheses.

KEYWORDS. Altered states of consciousness, short-term memory, creativity, holonomy, music appreciation, jazz, neurocognitive effects of cannabis, language, musical improvisation, music composition

INTRODUCTION

The ongoing public and scientific debate, and the political and law-enforcement conflicts concerning the proven and significant ther-

Peter Webster is Review Editor of the *International Journal of Drug Policy*, Quartier Les Vignes, Auvare Puget-Theniers, 06260 France (E-mail: vignes@monaco.mc).

apeutic uses of cannabis may be one of the more absurd spectacles of modern times. This debate, and indeed, the results of much recent research on marijuana, thought to be "scientific" by many, serve mainly to illustrate the pitfalls that have always confounded those who believe they can hold objective views on a controversial topic that do not fall prey to the political, moral, and religious prejudices of their times. As history plainly indicates, only a few gifted thinkers of any age seem inherently immune to such self-deception.

A major result of such prejudice has been the denial of effective medicine to no small number of those in need. But perhaps more importantly, contemporary attitudes both public and scientific have completely ignored or even actively rejected age-old uses of the natural psychoactive plant above and beyond the medicinal, uses that provide not a restoration, but rather an addition to, a valuable change, or even augmentation of normal human capacities. The suggestion that any "drug of abuse" might be used as a tool to enlarge one's experience and understanding, however, has attained the status of religious heresy and taboo in the minds of many, even among scientists who believe themselves beyond such irrationality. On the general principle that an agent that reliably alters a phenomenon must provide useful experimental possibilities, at the very least the study of cannabis-produced altered states of consciousness should prove worthwhile for understanding aspects of human psychology and cognition. The rarity of scientists who might entertain such a principle when applied to "illicit" psychoactive drugs must arouse the suspicion that the widely-acclaimed objectivity of the modern scientific enterprise is not as exalted as purported to be.

Although research on the extra-therapeutic uses of marijuana will not soon be undertaken in the hallowed institutions now too-often helping to prolong our ignorance on the subject, informal and private experimentation, seldom published, has been taking place. The results of such research is, as a rule, very speculative and provisional, and tends to be dismissed with a sniff by accredited academics, not to mention officials and policy-makers clinging to prohibitionism as if to a life-raft in a storm. However, this is not the first instance in the history of scientific exploration in which some of the more interesting research has been driven underground.

As an example of such unofficial, unpublished, and underground research, I would present the following speculative exploration on

marijuana consciousness and its relation to the appreciation and production of music. Hypotheses will be offered for consideration concerning the neurocognitive changes brought about by cannabis and how they may produce various useful effects. Since I have lived in Europe for many years, where the use of cannabis has been decriminalized in some countries, I can without legal risk or moral disqualification admit that my personal experimentation with cannabis has provided a first line of evidence for the formulation of the following ideas. This formulation has occurred through "real time" introspection about the altered states of consciousness provided by cannabis, as well as considerable follow-up and study analyzing the cannabis state from the perspective of what is today somewhat dubiously known as "normal consciousness."

MUSIC APPRECIATION

One of the more remarkable effects noticed in the state of consciousness brought on by cannabis is a greatly enhanced appreciation of music (Goode 1970, Tart 1971). The effect seems to be almost universal, and does not seem to fade with experience in the use of cannabis, as do certain other effects typically noticed by novice users. Curiously, such perception of enhancement does not seem to make excessive demands that the music to be appreciated be good, bad, or indifferent, although I have observed that many persons originally interested only in pop music, have suddenly found during a cannabis session that more "serious" music has quite unexpectedly become interesting in ways both surprising and profound. Conversely, some who had previously rejected pop music as crude and trivial have come to appreciate it more through cannabis consciousness.

The resulting musical empathy is also quite durable, not requiring further drug exposure for its (at least partial) preservation. The magical and inspiring quality of a given piece, revealed under the effects of cannabis, remains magical and profound long into the future, whether or not it is ever again experienced under the influence. The net effect seems to be one of "opening up" a person to something previously merely ignored or overlooked. The enhanced appreciation is thus legitimized as something essential and "real" and not merely a "drug effect," something "artificial" that wears off with the waning of the altered conscious state. Cannabis consciousness thus seems to be a

state in which at least a few prejudices and predispositions may be temporarily suspended so that something long-ignored for whatever reason can be seen afresh, as if for the first time. And so it would seem that the marijuana experience can provide a kind of *cognitive training* that may subsequently help enlarge and enrich one's outlook in desirable and entirely voluntary ways.

PERFORMANCE AND CREATION OF MUSIC

Musicians (as well as other artists) have testified not only to enhanced appreciation of music and art in general through the use of cannabis, but additionally, some have insisted that these altered states of consciousness are useful and valuable to augment their creativity. One such musician has stated (Grinspoon & Bakalar 1993, pp. 171-72):

> Over the years marijuana has served as a creative stimulant to my work as a performer and my more occasional inspirations as a composer. Almost all my choral pieces and songs have been composed partly or wholly under the influence: melodic and rhythmic ideas just pop into my head during relaxed and happy moments–'points of creative release'–and these seminal ideas are formed into whole compositions over a period of days to years.

Although research verifying such claims is hard to accomplish in any meaningful or decisive way, it should be noted that research on creativity is itself a long-neglected area, and standard psychological testing or methods of testing musical abilities seem crude tools to apply to the situation. We should therefore not be too dismissive of "anecdotal evidence" when our ability to amass "hard data" is so limited. Some of the attempts to amass such data have been laughable, although quoted time and again to dismiss claims of enhanced creativity (Bloomquist 1971). Bloomquist recounts as his primary example (p. 369) the experiment of Dr. C. Knight Aldrich of the U.S. Public Health Service, as if it were a definitive dismissal of the hypothesis of enhanced creativity. But the experiment is quite absurd, not even using natural cannabis but "parahexyl compound, a synthetic marijuana-like substance" (Aldrich 1944, pp. 431-433). Although it may also be somewhat speculative to say, it would seem that creativity would surely be boosted by an enhanced appreciation and a partial suspension of preconceptions, no matter what the stimulus.

Of course, as with so many things in life, practice makes perfect, or if not perfect, more nearly so. Thus it is with listening to music, and certainly with the making of music, a life-long process of practice, but more than a few puritanical minds will be perturbed by my suggestion, nay, *my insistence*, that the principle applies to the use of cannabis as well! ''You have to learn how to use it, and patiently experience the upheavals in the mental realm,'' insists Henri Michaux (Michaux 1961, p. 63). It has long been obvious to me that many of the best minds of our time suffer from a ridiculous and self-imposed handicap by ignoring or even actively rejecting a great aid to thinking and creativity: the altered states of consciousness provided by cannabis and other age-old plant substances so revered by our forbears. When intelligently used they are tools both powerful and benign, both fickle and of great utility, and above all, they require some considerable practice in order to use them in a way commensurate with their potential. Thus much of the research (on creativity, for example), which has used the substances on subjects who have not had long opportunity to practice with the resulting states of consciousness, is rendered of limited value. Not until these time-honored aids to thinking and perception become once again widely used will we begin to know their true utility. If they were universally revered by our tribal ancestors, and played an important role in the social and psychological evolution of our species as some researchers suspect (Wasson, Hofmann & Ruck 1978; Ott 1997), we may find them of even more value in a time when our technological powers have advanced maximally, but our moral sense of how to control great power for the common good has advanced little, if at all, since the Bronze Age.

ALTERED STATES OF CONSCIOUSNESS

Thanks to Prohibition, there has been insufficient serious research concerning the cognitive mechanisms and brain structures involved in the altered states of consciousness produced by marijuana and other such substances, and even research on the neurocognitive and psychological foundations of music, art and creativity has been frequently considered a study of the superfluous. Music and art for us moderns, unlike for our aboriginal ancestors, is seen as mere decoration, ''entertainment,'' an activity of leisure and play (indeed, music is *played*). Our scientific institutions thus seem to believe that the study of such

phenomena is of less importance than that of more "serious" undertakings. Apart from what limited scientific investigation has been accomplished, it seems that both the performance and perception of music involve the use of areas in the right hemisphere of the brain analogous to the speech comprehension and production areas of the left hemisphere, notably the famous Broca and Wernicke brain areas, and that these analogous right-brain areas might function similarly to the language centers of the left in the production and perception if not appreciation of music (Popper & Eccles 1983; Luria 1980). Indeed, music is depicted as a linear *symbolization* comprised of sequential interrelated unitary elements representing or, alternatively, evoking the perception of a durational and holonomic conception that seems an analogous phenomenon to language in many important ways.

Now another of the most noticed effects of cannabis consciousness, and one most pronounced and typical, is an alteration in short-term memory (Zimmer & Morgan 1997). Prohibitionists and others (who mistrust not only cannabis consciousness but apparently even the idea that changed consciousness is something worthy of scientific study) have seized on the short-term memory effect in their attempts to discredit cannabis and strike terror into the hearts of its users by implying that some kind of "permanent damage" must surely be happening when, in the middle of a sentence for instance, one forgets entirely what one was saying! But as all experienced cannabis users know, if at this point one simply relaxes a bit, sure enough, the memory soon is re-established, indicating that what has happened is not a *loss* of short-term memory or a damaging of the brain structures mediating it, but a different manner of retrieval. It appears that one's stream of consciousness merely *loses track* of trains of ideas that are quite normally being registered in short-term memory, perhaps because our perceptions require far more attention than normally, i.e., our consciousness is heavily involved with other matters than mere utilitarian attention to continuity of logical or linguistic thought processes. Our experience is so interesting and attention-consuming that we *ignore*, not lose, short-term memories. Indeed, the kind of short-term memory which scientists now study may be essentially a *linguistic* one, and other types of short-term memory, as yet unrecognized, may exist. They may be concerned with a more holonomic, rather than serially organized, linguistic way of contacting recent experience. The reality of the short-term memory effect might thus be to some extent an

artifact of current cognitive models and certain methods of psychological testing, and certainly should not be taken as evidence that cannabis produces deficit or damage.

SOME FURTHER HYPOTHESES

A hypothesis for the primary cognitive effect of cannabis might thus take these factors into account. If underlying or pre-conscious thinking processes are thought of as holonomic, all-at-once, in the nature of a Gestalt or unified whole, and language, and by analogous extension music, is a secondary and sequential representation of these pre-conscious *Gestalten*, we might hypothesize that cannabis effects some desynchronization or de-linking of the pre-conscious entities with the processes which translate them into symbolizations. The process seems cyclic or repetitive, the evolution of underlying *Gestalten*, and subsequent production of symbolizations proceeding with frequent breaks of the normal continuity of the process, and on several time scales simultaneously: a sort of cyclic forgetting of the pre-conscious by the conscious. The symbolization process, of forming a linguistic expression for example, might under the influence of cannabis "run away with itself" and become decoupled from the underlying gestalt which it represents. Thus, we "tend to forget what we are talking about" or even reading or thinking about, making reading a notoriously difficult task. This effect might well explain another of the peculiarities of cannabis consciousness: The character and meaningfulness of what is scribbled down while under the influence, although perhaps seeming profound at the time, is the next day notoriously silly and obvious. The symbolization has run away with itself and is no longer grounded or anchored to the holonomic patterns it represents.

However, what happens when the effect is practiced? Might it be put to some effective use? What if the person is talented with the mode of symbolization, i.e., is a poet, or novelist, or a musician? *Must* the output be silly? Might not a talent express itself under such circumstances in ways less attached to preconceptions? Extending these ideas further, perhaps the cyclic forgetting and decoupling of ongoing symbolization might be a factor in other important uses for cannabis. Might not the relief of some types of pain provided by cannabis occur because of a constant forgetting of its insult? If this be the case,

research aimed at producing analgesic cannabinoid preparations devoid of psychic effects may be a blind alley.

If this ignoring, or losing track of the mostly linguistic aspect of short-term memory is so universal, and the theory of music making and recognition being mediated by right-hemisphere areas analogous to those language-mediating areas of the left is valid, what happens to a musician when he plays music while under the influence of cannabis? Does he likewise forget what tune he is playing? Presumably if marijuana affects the language centres of the left hemisphere, even indirectly, it must similarly affect morphologically analogous structures of the right hemisphere. If marijuana consciousness does indeed affect a musician's perceptions and performance in some such way, how might that affect his music? And if a group or class of musicians who made a practice of using cannabis were so affected, how might that affect their collective concept of music and the way their music form developed? These might seem questions for research that in such a utilitarian age as our own will never be addressed. Yet perhaps the history of music already provides some hints.

TWENTIETH-CENTURY MUSIC

The history of music in the 20th century is, in one sense, a history of a bifurcation of music into two distinct methods of music making. The long tradition of Western music has emphasized the importance of music *composition* and the notation and publication of such compositions as opposed to the subsequent *performance* of these written compositions. The role of the composer and the performer are distinctly separate, and it is the composer, especially for orchestral works, who is considered to have done the lion's share of creating. The performer may "interpret" a written work of music with changes to tempo, dynamics, and general feeling, but any excess is considered bad form. All this of course has its parallel in language in the writing and reading of books. In our collective modern view, the greatest things that have been said are those written in stone, or at least in great books, and extemporaneous speech, as moving as it may be, is again, more often like entertainment than philosophy. When a piece of music has been *composed*, and when a linguistic expression has been *written down*, we seem automatically to attach more importance to it.

In the early decades of the 20th century however, the diverse in-

fluences in America, particularly of African origin, led to a form of music in which the performer himself took over the role of the composer to a significant extent, and jazz music became a form in which *improvisation* became a central aspect of the music. Although improvisation understood in its strict sense is "neither unique nor essential to jazz" (Harrison 1980, volume 9, p. 561), the shift of emphasis from the written composition to the performance of a piece as the principal creative act reveals that improvisation may in a larger sense consist of an ongoing evolution of a piece of music. Although a given performance of a jazz piece may not differ significantly from its previous performance, and thus the solo improvisations therein being practically repeated note for note, the performance does however differ drastically from another musician's or jazz band's rendering *of the same tune*. Thus each musician or group performs an improvisatory act over time with a given piece so that a standard such as *Body and Soul* performed by Ben Webster is an entirely different creative act than the same tune performed by Art Pepper, and the performances express correspondingly different emotional and intellectual gestalts. By contrast, two different performances of a Beethoven symphony are likely to represent and evoke very similar artistic and creative perceptions.

The improvised jazz solo is the central aspect of a piece, and expresses something new, if not every time, than at least for a given musician or group playing a given piece. Jazz improvisation, whether realized in a solo or in an evolved way of playing a piece as a whole, expresses something relevant to the current emotional and intellectual state of the musician-as-composer, and his interaction with his audience. The improvised tune becomes a mere vehicle for the artist and its performance resembles the musical equivalent of an ancient linguistic form, *story-telling*. A performer takes an eternal theme and embellishes it for the present moment, for the benefit of his listeners, to make the universal history and mythology of the tribe manifest in the present, and informative of current interests and concerns.

Was this 20th century musical development merely a throwback to primitive forms by uneducated and underprivileged musicians who rejected Western traditions in music? Hardly. The great jazz musicians routinely know much about the traditions and technical structure of composed music to an extent that classical musicians envy. And the technical virtuosity of many jazz musicians often surpasses all normal requirements of the Western tradition (Mingus 1972):

> There are many other instruments besides the trumpet which jazz musicians have made do the impossible. And they can play, for hours on end, technical, involved, difficult, educated lines that have melodic sense. They are all virtuosi. The same goes for string bass. The same goes for saxophone, although it is not used much in symphony. But anything Milhaud has done in classical music, McPherson and Bird, alone, do with ease as well as human warmth and beauty. Tommy Dorsey, for example, raised the range of the trombone two octaves. Britt Woodman raised it three. And take Jimmy Knepper. One of his solos was taken off a record of mine and written out for classical trombone in my ballet. The trombone player could barely play it. He said it was one of the most technical exercises he had ever attempted to play! And he was just playing the notes–not the embellishments or the sound that Jimmy was getting.

JAZZ AND REEFER

From the 1920s to the 1940s, the very period in which improvisation in jazz was becoming the central creative aspect of the music, jazz musicians almost universally enjoyed cannabis, and we have many personal attestations and historical documents to prove the case. One particularly rollicking book about the epoch, and the wild times and great music that resulted, is Mezz Mezzrow's *Really the Blues*, and Mezz was himself not only a great jazzman, but famous for the excellent quality marijuana of which he seemed always to have a large supply (Mezzrow & Wolfe 1946)! A reading of personal reflections about the use of marijuana by jazzmen of the time indicates that the herb was often used as a stimulus to creativity, at least for practice sessions, many such as Louis Armstrong praising its effects highly. The widespread use of cannabis by jazz musicians of the time is even revealed by the campaign of Harry Anslinger and his Bureau of Narcotics to demonize marijuana. At one point he issued a directive to all his field agents, as related in the following story from a speech by Charles Whitebread, Professor of Law, USC Law School (Whitebread 1995):

> After national marijuana prohibition was passed, Commissioner Anslinger found out, or got reports, that certain people were violating the national marijuana prohibition and using marijuana

> and, unfortunately for them, they fell into an identifiable occupational group. Who were flouting the marijuana prohibition? Jazz musicians. And so, in 1947, Commissioner Anslinger sent out a letter, I quote it verbatim, 'Dear Agent So-and-so, Please prepare all cases in your jurisdiction involving musicians in violation of the marijuana laws. We will have a great national round-up arrest of all such persons on a single day. I will let you know what day.'

Is it possible to attribute some causative connection between the cognitive effects of cannabis of which we are now becoming scientifically aware and the development of creative jazz forms of the 1930s and 1940s? To return to my previous question, if high on marijuana does a performing musician "lose track" of the composition he is playing much as one might lose track of the thread of a conversation? Did cannabis consciousness thus play a role in bringing improvisation to the fore?

In fact, experienced cannabis users who are well aware of the "short-term memory effect" become quite adept at counteracting it. In all probability extensive practice with cannabis consciousness allows the user to not only counteract such effects, but use them in positive ways. A temporary and momentary "forgetting" of the limiting structures of either an ongoing conversation, or of a musical piece, when such an effect has been practiced might well be just the right influence to bring improvisation to the fore, both in music and conversation or writing. It is my view, therefore, that the cumulative and long-term practiced use of cannabis by virtuosi jazz musicians was a certain and positive factor in the evolution of the music.

My experience with music indicates that it would of course be silly to say that jazz musicians of the period were literally forgetting what tune they were playing, and through such constant forgetfulness arose a great musical innovation! But as with the practiced user of cannabis who learns to counteract the short-term memory effect and use it to advantage, I would more realistically propose that a similar thing was happening *collectively* and *incrementally* within the fairly small community of jazz musicians of the time, a community more like a family than a world-wide diversity of people and schools as it has become today. The jazz community of the time constantly practiced together, brainstormed together, performed together, and smoked marijuana together. As a cumulative effect, it is my contention that the practiced

use of cannabis provides a *cognitive training* that assists and accentuates the improvisational, creative frame of mind much as other kinds of study or training shape abilities and perfect talents. It is not that cannabis consciousness *itself* ''produces'' ideas that are creative, or that valuable ideas come *during* the experience or *because of* it, but that cumulatively, over time, *the kind of perception and thinking initiated by cannabis* leads one to be generally more open to alternative and perhaps *adventurous* ways of seeing things which enrich normal consciousness. Normal consciousness, as we all admit, is limited in often involuntary, invisible ways by our times, customs, prejudices, by the necessary ignorance we must cultivate to cope with modern life. Cannabis very probably contributed to, or was used as a tool to facilitate the jazz revolution in music, and might be similarly used to facilitate important advances in any other area of human interest where creativity and adventurous thinking are important. The understanding of human consciousness and the nature of altered states of consciousness come immediately to mind.

And as for literally forgetting what piece one is playing, biographies of great musicians often tell of experiences when they were required to bluff it through with some extemporaneous inventions. The great French jazz pianist Martial Solal tells of such a concert he gave in his youth, it was to qualify for an important prize and at the climax of the classical piece he was playing his mind went blank, but his forced improvisation was so good that the judges didn't even detect his bluff! It was at that point, he says, that he decided that jazz rather than classical music was to be his future.

So perhaps jazz musicians literally did often encounter some short-term memory effects, and had often to ''bluff'' it. With virtuoso musicians, such bluffing is unlikely to fall into something less than proficiency, and from what experienced users of cannabis all say, the ''bluffing'' seems to result in an unprecedented creativity: In a sort of Zen manner, what comes out of the virtuoso when he abandons his calculated intentions and practiced routines is not nonsense but often his finest creation! If a mere plant can assist the forgetfulness which is the germ of spontaneous creativity, many of the greatest minds of our time surely *are* missing the beat by rejecting not only its use but by assisting to prevent others from doing so. They thus prove once again that even genius is capable of the narrowness thought characteristic of the uneducated.

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Introduction:
Cannabis Therapeutics in HIV/AIDS, Plus, a Modest Proposal

The *Journal of Cannabis Therapeutics: Studies in Endogenous, Herbal and Synthetic Cannabinoids* is pleased to present its first special issue, on the subject of *Cannabis Therapeutics in HIV/AIDS*. Certainly, with respect to therapeutic cannabis, HIV/AIDS sufferers are its most common consumers, and this is a topic most worthy of closer examination. Our current offering includes numerous articles pertinent to the issue, which will be supplemented by subsequent entries in future volumes.

The survey commences with a broad medical overview of the subject by Dr. Richard Bayer. This ably serves as a point of departure in its presentation of the pertinent topics of interest with respect to AIDS and its treatment.

Next, Clint Werner offers a distinct viewpoint, more of an "insider's view" on the twenty-year history of this affliction, and its interface with cannabis and the medical marijuana political movement.

Subsequently, we present two survey studies of clinical cannabis usage from different populations in California. Both confirm the assertion above that HIV/AIDS sufferers frequently turn to cannabis in attempts to treat their symptoms. The first is from Dr. Stephen Sidney, a physician and epidemiologist working for Kaiser Permanente, the state's largest HMO (Health Maintenance Organization). The second is from Valerie Corral, a clinical cannabis patient herself. Despite the fact that she is not from a professional background, her long-term study provides much useful information on the range of conditions, symptoms and results obtained with medical marijuana.

Dr. Guy Cabral provides us with a state-of-the-art review of immunological issues in cannabis usage. The picture is a cautionary one, but also one that pro-

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vides no blanket support or indictment of therapeutic cannabis with respect to immune effects. As always, more research is needed to ascertain all the medical implications inherent in this treatment modality.

Donald Tashkin provides another thorough review, this time of pulmonary issues with smoked cannabis that is of particular import to HIV-positive patients.

Early issues of *JCANT* have alluded to possible synergistic effects of cannabis components beyond THC. The following article by McPartland and Russo examines those "other players" in greater detail in an effort to elucidate the issue.

Moving into the area of harm reduction, Dr. Franjo Grotenhermen provides a clinician's interpretation of cannabis consumption issues, and a number of practical recommendations for patients and their doctors.

Dr. Dale Gieringer provides some of the first experimental data on the method of cannabis vaporization that portends to provide the same clinical benefits as smoking, but with markedly fewer health sequelae. This is a technology under intense scrutiny among clinical cannabis patients and advocates, but one hardly mentioned by the recent Institute of Medicine Report (Joy, Watson, and Benson 1999).

A research group from the University of Mississippi with lead author Susan Broom provides an experimental study examining another alternative cannabinoid delivery system, that of rectal suppositories containing THC-semisuccinate.

Rounding out the original articles, Drs. Brian Whittle, Geoffrey Guy and Philip Robson of GW Pharmaceuticals provide a glimpse of innovative research in the UK focusing on standardized sublingual whole-cannabis extracts, and aerosol preparations that many believe represent the future of standardized pharmaceutical cannabis delivery.

AIDS IN THE THIRD WORLD: A MODEST PROPOSAL

Since its discovery a mere two decades ago, acquired immune deficiency syndrome (AIDS) has quickly become one of the world's most challenging public health issues. Initial cases in the USA and Europe mostly affected homosexual males and intravenous drug abusers, making it easy for those in some quarters to relegate AIDS to some expression of heavenly revenge for immoral behavior. This introduced a noteworthy roadblock into funding for research (see Werner's article in this issue). When "innocent victims" such as transfusion recipients and babies with congenitally acquired infections appeared on the scene, public sentiments began to change. Soon enough, the disease proved to be a pandemic, and none was immune to its reach. It now affects 36 million people worldwide (Piot et al. 2001).

The current spread of AIDS is greatest in the Third World, with 60% of total cases in Africa, affecting an estimated 8% of the adult population (Thomas

2001). Transmission is primarily through heterosexual sex and vertical transmission. Asia seems to be the next nidus for its spread, which has recently been termed "explosive" (Kilmarx et al. 2000).

Treatment of AIDS remains extremely problematic, particularly in the Third World, due to the incredible expense of retroviral and newer protease-inhibitor drugs. These costs easily reach into the many thousands of dollars per patient per year.

Benefits of cannabis on appetite have long been known, including early citations by da Orta in India in his 1563 book (da Orta 1913), and Owen in the USA (Owen 1860). Sir William Dixon (1899), a noted pharmacologist, said of smoked cannabis (p. 1356), "It is not dangerous and its effects are never alarming, and I have come to regard it in this form as a useful and refreshing stimulant and food accessory, and one whose use does not lead to a habit which grows upon its votary."

The modern history of cannabis as an anti-anorexic and antiemetic is addressed in the current issue, along with two excellent reviews in the *JCANT* charter issue (Hollister 2001; Musty and Rossi 2001). Given the current support for this indication, and an overwhelming need for less expensive medicine to treat AIDS symptomatically until a cure is available, one might properly ask the question, "Why not cannabis?"

International law governing "illicit drugs" is contained within the United Nations Single Convention Treaty on Narcotics (United Nations 1961, available online at: *http://www.druglibrary.org/schaffer/legal/singconv.htm*).

Although international trade on cannabis is prohibited, existing provisions of the treaty allow for internal medical usage, or its abrogation in the event that the treaty contravenes a nation's constitution or its expression of human rights. That would certainly seem to be the case with AIDS. Increasingly, this treaty has proven counter-productive to the public health, and a key promotional factor in the highly wasteful and ineffectual international "War on Drugs." A modest proposal would call for its revocation, or at the very least, its amendment to allow for therapeutic cannabis usage as a stopgap effort in treatment of the worldwide AIDS epidemic.

Ethan Russo, MD

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Therapeutic Cannabis (Marijuana) as an Antiemetic and Appetite Stimulant in Persons with Acquired Immunodeficiency Syndrome (AIDS)

Richard E. Bayer

SUMMARY. Acquired immunodeficiency syndrome (AIDS) is a common cause of death among young adults in the USA. AIDS wasting syndrome is the most common clinical presentation of AIDS. Antiretroviral drug therapy has improved the prognosis of persons with AIDS, but also contributed side effects, particularly nausea and anorexia. Case reports demonstrate persons with AIDS use cannabis as medicine to control nausea, anorexia, and pain, while noting improved mood. Recent clinical research comparing smoked cannabis to oral dronabinol (synthetic THC or Marinol) demonstrates no immune dysfunction in persons using cannabinoids and positive weight gain when cannabinoids are compared to placebo. Harm reduction research indicates that heating cannabis to temperatures well below combustion ("vaporization") yields active cannabinoids and a significant reduction or elimination of toxics (benzene, toluene, naphthalene, carbon monoxide, and tars) commonly found in smoked cannabis. More research is indicated but vaporizers appear to substantially reduce what is widely perceived as the leading health risk of cannabis, namely respiratory damage from smoking. In spite of a need for more rigorous scientifically controlled research, an increasing num-

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Richard E. Bayer, MD, FACP, is board certified in internal medicine and a Fellow in the American College of Physicians–American Society of Internal Medicine. He lives in Portland, Oregon (E-mail: ricbayer@home.com).

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ber of persons with AIDS are using cannabis to control nausea, increase appetite, promote weight gain, decrease pain, and improve mood.

KEYWORDS. Cannabis, marijuana, dronabinol, THC, Marinol, AIDS, HIV, harm reduction, immunodeficiency, vaporization, vaporizer, wasting, anorexia, nausea, appetite, pain

AIDS IN THE UNITED STATES

The history of acquired immunodeficiency syndrome (AIDS) began in 1981 when the first five cases of AIDS were reported in the United States. Shortly thereafter, the disease was categorized as an epidemic. In 1984, the etiology of AIDS was found to be an RNA virus called human immunodeficiency virus (HIV). In 1985, a sensitive enzyme-linked immunosorbent assay (ELISA) was developed, and clinical testing for antibodies to HIV became possible.

By 1993, the United States Department of Health and Human Services (DHHS) listed AIDS as the most common cause of death among men aged 25 to 44 years (US DHHS 1995). By the end of 1998, the United States Centers for Disease Control and Prevention (CDC) estimated that nearly one million Americans had contracted HIV infection, one-third of whom were unaware of their affliction (CDC 1999).

By the end of 1999, a total of 733,374 cases of affected persons with AIDS (PWAs) had been reported to the CDC. Demographics revealed that 82% were men, and 18% were women. Only 1% were children less than 13 years of age. Forty-three percent of persons with AIDS were white, 37% black, 18% Hispanic, < 1% Asians and Pacific Islanders, and < 1% American Indians and Alaska Natives. Forty-seven percent of persons with AIDS were men who have sex with men, 25% were injection drug users, 10% were persons infected heterosexually, and 2% were persons infected through blood or blood products (CDC 1999).

HIV destroys CD4+ T lymphocytes, and laboratory measurements of "T Cells" indicate immune system damage. More recently, the technology of polymerase chain reaction has allowed the actual measurement of HIV RNA blood levels or "viral load" and this parameter is increasingly utilized clinically to help determine when to initiate and modify antiretroviral therapies (Saag et al. 1996).

The surveillance conditions for diagnosis of severe HIV disease or AIDS were originally defined by the CDC prior to the identification of HIV as the etiologic agent. Although surveillance criteria have changed over the years, the clinician should view HIV disease as a spectrum of illness that ranges from a primary infection, to the asymptomatic infected, to advanced disease or AIDS, which causes marked morbidity and mortality (Fauci et al. 2000).

For surveillance purposes, AIDS is defined by indicator diseases such as the AIDS wasting syndrome, *Pneumocystis carinii* pneumonia, or Kaposi's sarcoma in young adults. AIDS is identified in asymptomatic persons by laboratory tests such as CD4+ T lymphocyte counts of less than 200/mcl or a CD4+ T lymphocyte percent of total lymphocytes less than 14 (CDC 1992). Since 1992, scientists have estimated that about half the people with HIV develop AIDS within 10 years after infection, but this time varies greatly from person to person (CDC 2000).

AIDS wasting syndrome is an AIDS-defining condition, identified when a patient manifests involuntary weight loss of more than 10% associated with intermittent or constant fever and diarrhea or fatigue for more than 30 days in the absence of a non-HIV explanation. It is the initial AIDS-defining illness in 9% of patients with AIDS in the United States and thus is currently the leading initial clinical indication of AIDS (Fauci et al. 2000).

Standard antiretroviral treatments for HIV infection, such as zidovudine (AZT or ZVD) or lamivudine (3TC) can cause significant nausea. Treated patients often have difficulty maintaining baseline weight. In 1996, the United States Food and Drug Administration (FDA) approved the use of protease inhibitors, which when taken in combination with standard antiretroviral drugs can reduce viral load and markedly slow the progression of HIV/AIDS disease (CDC 1998).

A concern for many who take protease inhibitors is that the side effects can be more severe than those associated with standard antiretroviral drugs. As occurs with some persons receiving chemotherapy for cancer, patients with AIDS often find that the medicines they need to sustain their lives can produce side effects so intolerable that they become reluctant to maintain their treatments, or fail to take treatment regularly. This can be dangerous, for failure to maintain a regular medication schedule can lead to the development of treatment-resistant strains of HIV (CDC 2000).

CANNABINOIDS AS ANTIEMETIC AND APPETITE STIMULANT IN AIDS WASTING SYNDROME

Ethnobotany documents important medical uses of herbs, including cannabis (Russo 2000), but the first modern placebo-controlled trial that demonstrated efficacy of THC as an antiemetic in cancer chemotherapy was published

in 1975 (Sallan et al. 1975). In the 1970's and 1980's, six American states engaged in clinical trials of smoked cannabis and oral THC to control nausea and emesis from cancer chemotherapy. These trials involved 748 persons who smoked cannabis and 345 patients who used oral THC capsules, and demonstrated that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy (Musty and Rossi, 2001). A synergistic relationship of the combination of THC and the antiemetic prochloperazine was more effective than either drug alone, as suggested by past studies (Hollister 2001). These are important findings, because our most efficacious modern antiemetics, including well-tolerated serotonin antagonists like ondansetron (Zofran), promise only about 80% efficacy (Zofran package insert). In other words, in one out of every five treatment episodes, our best antiemetics demonstrate no efficacy. Although no studies have been done comparing ondansetron to cannabis, patients would be well served by studying efficacy of cannabinoids alone, or in combination with other antiemetics in persons who currently cannot control nausea and emesis with modern serotonin antagonists like ondansetron.

In 1992, the FDA approved the use of Marinol (dronabinol or synthetic THC) for the treatment of AIDS wasting syndrome. Dronabinol has been shown to stimulate appetite, promote weight gain and improve mood in persons with AIDS in short term studies (Beal et al. 1995), while maintaining effectiveness and safety over during a longer (12 month) study (Beal et al. 1997). Marinol is usually prescribed at a dose of 2.5 mg by mouth 2 to 3 times daily before meals to improve appetite (Roxane Labs 1999). Although the Drug Enforcement Administration (DEA) originally listed dronabinol as a Schedule II drug, it was recently moved to Schedule III, which may increase the likelihood of American physicians prescribing it.

While dronabinol is the only cannabinoid that physicians can legally prescribe in the USA, it remains extremely expensive (often $600 to $1200 US each month), has a slow onset of action because it can only be taken orally, and has a relatively high incidence of side effects (particularly dysphoria), so that many patients prefer herbal cannabis. As is the case in many cancer patients, people with AIDS frequently expressed a preference for smoked cannabis over dronabinol because it provides results with smaller doses and fewer undesirable side effects. In addition, some persons report better symptom control consuming cannabis rather than dronabinol, which may be related to the additional cannabinoids, such as cannabidiol, that are found in cannabis but not in dronabinol (Grinspoon et al. 1997).

Other agents used to treat AIDS wasting include anabolic steroid hormones such as the progesterone megestrol acetate (Megace), tested alone and in combination with dronabinol (Wright et al. 1997), and androgenic steroids such as oral oxandrolone (Berger et al. 1996), or intramuscular testosterone

enanthate (Grinspoon et al. 1998). More extreme options include human growth hormone, which can cost over $150 daily, and total parenteral nutrition, which is expensive, invasive, and medically risky (Krampf 1997). The above treatments have shown some successes, but all have drawbacks, and thus treatment must be individualized to meet each patient's needs.

For a more comprehensive discussion of cannabis as antiemetic and appetite stimulant, readers are referred to Leo Hollister's review, "Marijuana (Cannabis) as Medicine." in the charter issue of *Journal of Cannabis Therapeutics* (Hollister 2001). For a comprehensive clinical discussion of HIV disease, readers are referred to an internal medicine textbook such as *Harrison's Principles of Internal Medicine* (Fauci et al. 2000).

CASE REPORTS (THE PATIENTS' PERSPECTIVE)

There are many case reports from persons with AIDS who benefit from adjunctive use of cannabis to stimulate appetite, control pain, and improve quality of life (Zimmerman et al. 1998; Grinspoon et al. 1997; Krampf 1997).

Patient S.C. describes:

> Within eight months, beginning in 1995, I was hospitalized three times for pneumonia and sinus infection. I'd been feeling pain and congestion in my chest, and then I began having trouble breathing. I was still taking AZT and they put me on antibiotics and prednisone for the pneumonia. It was so difficult for me to swallow the pills. Almost immediately after taking them, a violent nausea would set in. I couldn't eat or hold down any food. After a few weeks of this, my weight dropped down from 150 to 115 pounds.
>
> I did what I could during that time to get relief. That's when I realized, almost coincidentally, that marijuana alleviated my nausea. When I took a few hits of marijuana, I felt better within five to fifteen minutes. It also gave me back my appetite. In a short time, I gained back almost all my weight, and I began feeling much healthier.
>
> Just as importantly, my marijuana use would help me deal with the new drugs I'd soon be taking. They began combining AZT and another anti-viral drug, called 3TC, with a protease inhibitor called Crixivan . I did notice a gradual improvement in my health, and my T-cell count started coming up. But the nausea I experienced was worse than anything I had felt with AZT alone. It was indescribable. It didn't seem like I had many choices though. I knew I needed these medicines to stay alive, even though the nausea they caused me was unbearable. So, I kept taking them, along with marijuana to control the nausea.

> I have to tell you that I sincerely doubt I could have continued the treatment without marijuana. This is very important because, while there is no cure for AIDS, I believe these medications have actually reversed my disease and saved my life. What marijuana did, aside from making me feel better, was make these drugs tolerable for me.
>
> Right now, my weight is up to 148 pounds. I take 16 pills a day, and I smoke marijuana before each meal to quell the nausea and stimulate my appetite. About one-half hour before I want to eat, I take three or four puffs. Usually, in about 20 minutes, I get the munchies and then I want to eat. It's still a struggle sometimes, but I'm healthier, stronger, and I enjoy living. (Zimmerman et al. 1998, pp. 48-49)

Patient G.S. summarizes his experience:

> Even if I was not recovering [from AIDS], the relief would have been worth any bad effect the marijuana might have had. I could keep down food, and I could stop the aching. Also, I'm convinced that one of the worst things for my immune system was the stress my sickness caused me. Marijuana reduced my stress and it calmed my soul. It made me not worry so much about the difficult regimen of pills I had to take, or how I was going to get to the grocery store because I didn't think I'd be able to walk. Marijuana allowed me to accept the possibility that I might die, and yet, I believe, because I smoked marijuana, I lived. (Zimmerman et al. 1998, p. 53)

In the US, many persons with AIDS use cannabis daily to control nausea, increase appetite, decrease pain, and improve mood. Although case reports like those above are frequent, the federal drug bureaucracy has kept a virtual stranglehold on all clinical research into the safety and effectiveness of cannabis (Doblin 2000).

RECENT CLINICAL RESEARCH ON CANNABINOIDS, IMMUNITY, AND WEIGHT GAIN

After an Byzantine ordeal that lasted the better part of a decade (Doblin 2000), University of California-San Francisco (UCSF) researcher, Donald Abrams, MD, was finally able to do a study to compare the effectiveness of dronabinol (Marinol) versus smoked cannabis versus placebo in persons with AIDS.

The results of Dr. Abrams's study, "Marijuana does not appear to alter viral loads of HIV patients taking protease inhibitors," were released July 13, 2000 by UCSF (Abrams 2000). The study found that patients with HIV infection

taking protease inhibitors do not experience short-term (3 week) adverse virologic effects from using cannabinoids.

Of the 62 subjects who completed the inpatient study, values for 36 with undetectable HIV RNA levels remained unchanged through the trial. All 26 subjects with detectable HIV RNA levels experienced declines in those levels. Of those, the subjects who smoked cannabis or took oral dronabinol experienced slightly greater decreases in HIV RNA levels than did subjects who took the placebo, but there was no statistical difference between the three groups.

All three groups gained weight, thanks to regularly scheduled meals and available snacks. However, the subjects in the placebo arm gained an average of 1.30 kg, while those who took oral dronabinol gained an average of 3.18 kg, and those who smoked cannabis gained an average of 3.51 kg. These results should alleviate some concerns about the effects of THC as dronabinol and smoked herbal cannabis on immunity,

CANNABIS AND HARM REDUCTION STRATEGIES FOR PERSONS WITH AIDS

There is concern about risk of potential respiratory and lung infection in immunocompromised persons from smoking cannabis because underground market sources may be contaminated with bacteria or fungal spores. Some patients minimize this risk by cultivating their own cannabis, while others are careful to obtain cannabis only from trusted sources. Some persons heat the cannabis in a toaster oven for several minutes to reach the temperature used to pasteurize milk, 71°C (160°F), but keep the heat much lower than the 140°C to 190°C (284°F to 374°F), at which temperature the cannabinoids "vaporize" or "volatize" causing significant degradation of source material (Rosenthal et al. 1997; Gieringer 2001).

These are descriptions of some patients' strategies, but there are no controlled trials demonstrating increased risk for infection in cannabis-only smokers versus nonsmokers among persons with AIDS or any documented clinical benefit from attempting to sterilize the cannabis as described above.

Some patients try to reduce the risk of using contaminated cannabis by alternately smoking cannabis and cooking it in food. Some books on medical use of cannabis contain recipes (Rosenthal et al. 1997), or alternatively, patients may use a standard search engine on the Internet. Patients sometimes rely on smoked cannabis when the symptoms of nausea are so severe they are incapable of oral intake, but at other times, bake it into brownies or put in other food. In this way, the patient may get the immediate and effective relief that smoking provides, but when the need is less pressing, minimize the risk of smoking potentially contaminated cannabis through oral intake.

Oral ingestion of cannabis resolves the issues of smoking toxicity, but the harm-reduction issue is complicated by the United States' War on Drugs, which causes a "prohibition tariff" and increases cost by a factor of about 10. Estimates are that without cannabis prohibition, production costs would be \$30 to \$40 per ounce (Grinspoon 1997), but current street prices are about \$300 to \$400 per dry ounce for high-quality female flowers ("bud"). Eating cannabis, or making tea is expensive, and as for dronabinol, it has a slower onset of action. Oral THC also produces lower blood levels, and is less effective in controlling nausea when compared to smoked THC cigarettes (Chang 1979).

Inhalation of therapeutic drugs, such as treatment of asthma using metered dose inhalers, provides rapid onset of action and dose titration using the minimum effective dose (which minimizes drug side effects). Medical inhalation of cannabis provides similar advantages, but without vaporization, carries the risk of inhaling smoke. Therefore, one method to reduce harm from smoking is for patients to use only high medical quality cannabis, so there is a greater concentration of therapeutic cannabinoids per mass ingested.

Promising initial results from a study by California NORML (National Organization to Reform Marijuana Laws) and the Multidisciplinary Association for Psychedelic Studies (MAPS) demonstrate that patients may be able to protect themselves from harmful toxics in cannabis smoke by inhaling their medicine using an electric vaporizer (Gieringer 2001). Vaporization involves releasing cannabinoids by heating cannabis to temperature short of combustion, thereby eliminating or substantially reducing harmful toxics that are present in cannabis smoke. Gieringer reports traces of THC appearing at temperatures as low as 140°C (284°F) while significant amounts of benzene did not appear until 200°C (392°F) and combustion did not appear until around 230°C (446°F) or above. An aromatherapy device called the Volatizer (*www.volatizer.com*) consisting of an electric heating element similar to an automobile cigarette lighter on a metal wand produces a temperature of 185°C (385°F) and is placed over the bowl of cannabis that sits inside the top of a 0.5 liter side-arm Erlenmeyer flask. Vapors are inhaled through a rubber tube connected to the side-arm of the flask. The Volatizer reduced measured toxics (benzene, a known carcinogen, plus toluene and naphthalene), carbon monoxide, and tars when compared to combusting the cannabis by flame. More research is indicated, but vaporizers appear to substantially reduce what is widely perceived as the leading health hazard of cannabis, namely respiratory damage from smoking. Drawbacks to vaporization include cost (a complete Volatizer unit costs \$250 US), and portability. Competing aromatherapy devices include using a thermocouple heat gun blown across the cannabis and collecting vapors in a chamber or bag (*www.mystifier.com*) or placing cannabis in one end of a small (pencil size) glass tube with the other end of the glass tube connected to a

plastic tube for inhalation. The glass end with cannabis is then inserted in an "oven" that looks like an automobile oil filter and vapors are inhaled through the plastic tube (*www.vaportechco.com*). These two units are less expensive (about $150 US) than The Volatizer but have not yet been laboratory tested. Other units are available, but until paraphernalia laws are relaxed and mass production of vaporizers is possible (e.g., using small batteries), vaporization remains an attractive but expensive harm reduction tool.

Simpler devices such as water pipes or "bongs" that combust the cannabis and draw the smoke through water before inhalation serve to cool the inhaled smoke, but there is no evidence that they reduce the ratio of tar and particulate matter to therapeutic cannabinoids (Gieringer 1994). There may be undiscovered health advantages from cooling the inhaled smoke or filtering out certain gases, but any advantage of a water pipe or bong over a joint to deliver smoked cannabis remains undocumented.

A medical records review of 452 daily cannabis smokers who never smoked tobacco showed a slight increase in clinic visits for colds, flu, and bronchitis over a 2 year period when compared to demographically similar group of non-smokers of either substance (Polen 1993). Although heavy cannabis smokers report "smokers' cough" (chronic bronchitis), there is no evidence that cannabis smokers who do not smoke tobacco will develop small airways disease, such as emphysema (Tashkin et al. 1997).

Patients should be advised to stop holding one's breath after inhaling smoke for this technique does not increase benefits from cannabis, but rather appears to increase risks of potentially dangerous deposits in the airways. Probably because the lifetime quantity of smoke consumed by cannabis smokers is typically far less than for tobacco smokers, there exists no clinical evidence that typical cannabis smokers have higher rates of respiratory cancer (Zimmer et al. 1997). However, recent reports from the United States (Zhang et al. 1999) and Europe (Carriot et al. 2000) suggest heavy cannabis smokers may increase risk of head and neck cancer with a strong dose-response pattern.

CONCLUSION

Many patients report that cannabis helped prolong their lives by enabling them to cope with some of the difficult symptoms and treatments associated with AIDS. In spite of a need for more rigorous scientifically controlled research, an increasing number of persons with AIDS are using cannabis because they find it controls nausea, increases appetite, promotes weight gain, decreases pain, and improves mood.

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Medical Marijuana and the AIDS Crisis

Clinton A. Werner

SUMMARY. The sudden emergence of the AIDS epidemic and the initial lack of effective treatments politicized the patient population into demanding quicker development of and access to promising medications. When numerous AIDS patients demanded marijuana to treat the anorexia and wasting syndrome resulting from both illness and medications, the federal government's Public Health Service closed the only legal source of supply. The federal authorities' abdication of compassion and repression of research spawned a grassroots political movement that repudiated federal regulations. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Acquired Immune Deficiency Syndrome (AIDS), HIV, cannabis, marijuana, medical marijuana, delta-9-tetrahydrocannabinol, AIDS-wasting syndrome, azidothymidine (AZT), dronabinol

The AIDS epidemic was a crucial influence on the growth of support for the medical marijuana movement. When federal officials responded to an increasing number of requests for marijuana from a growing population of AIDS patients by closing the Compassionate Use Investigational New Drug (IND) Program that supplied the drug, a grassroots political movement was launched to protect patients from arrest. The numbers of HIV-positive patients, the po-

Clinton A. Werner, BA, MLS, is the author of a forthcoming book on the history of the medical marijuana movement.

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litical prowess of AIDS activists and the frustrations of AIDS researchers had a profound effect on the revelation to the American public that, with regard to cannabis, the federal government favored prohibition over science and compassion.

The first hints of the coming epidemic appeared at the end of the 1970's and in early 1980 when doctors in New York City, San Francisco, and Los Angeles began to see rare and unusual illnesses appearing among young gay men. The June 5, 1981 edition of the Centers for Disease Control publication, *Morbidity and Mortality Weekly Report* printed the following notice (Center for Disease Control 1981, pp. 305-308): "In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at three different hospitals in Los Angeles, CA" the report also noted that, "*Pneumocystis* pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients." A second troubling *MMWR* alert soon followed that linked the development of a rare skin cancer, Kaposi's sarcoma, in gay men to the outbreaks of *Pneumocystis*. The following day news of the burgeoning epidemic was relayed to the general public by the *New York Times'* headline (Altman 1981), "Rare Cancer Seen in 41 Homosexuals."

The syndrome was quickly traced to a breakdown in the immune system, but the causative agent remained unknown. Panicky speculation attributed the dysfunction to everything from water fluoridation to marijuana contaminated with paraquat, a quaternary ammonium pesticide (Shilts 1987). Initially, the illness was referred to as Gay Related Immune Deficiency (GRID), but the appearance of GRID-related opportunistic infections among hemophiliacs, transfusion recipients and intravenous drug users confirmed that the infectious agent lacked specificity to sexual orientation, and it was renamed Acquired Immune Deficiency Syndrome (AIDS).

When AIDS emerged, researchers had no precedent or guide in dealing with this catastrophic collapse of their patients' immune systems. Without an identified causative agent, no treatments could be devised. Doctors were forced to pioneer treatment protocols, resorting to trial and error exploration of off label prescriptions for never-before-seen maladies such as opportunistic infections with *Toxoplasmosis gondii* and *Cryptosporidium parvum*. Dr. Donald Abrams, Assistant Director of the AIDS program at San Francisco General Hospital, recalled the early days of the epidemic (Bayer 2000, p. 70), "We didn't have anything to offer them. [They] died, and the deaths they died, I recall, were very terrible deaths; they were deformed and disfigured and wasted away, Kaposi's sarcoma lesions all over their bodies."

On April 23, 1984, the isolation of the human immunodeficiency virus (HIV) that causes AIDS was announced. Knowledge that the infectious agent is a retrovirus allowed investigators to target their search for effective treat-

ments. Due to the lengthy and involved Food and Drug Administration (FDA) drug approval procedure, however, any promising drugs that were developed were years away from availability. In the meantime, thousands would die without treatments for HIV. There were also myriad problems getting research under way.

There were two possible paths to drug availability: through government-sponsored clinical trials, or by research funded by pharmaceutical corporations in hopes of finding marketable products. Neither the government nor the private sector was eager to develop treatments for AIDS patients. The pharmaceutical companies did not envision that the numbers of AIDS patients would yield enough profits to justify expending millions of dollars on drug research and development (Arno 1992). The advent of AIDS also coincided with the inception of the Ronald Reagan Presidential Administration, which was committed to making deep cuts in domestic spending. Many of these policies adversely affected the ability of the nation's public heath service to respond to the type of public health catastrophe that AIDS was and remains (Shilts 1987).

The fact that the primary population affected by AIDS was gay men had a profound effect on the Reagan Administration's response to the crisis. President Reagan had decried homosexuality and trumpeted the right wing moralism of the Christian Coalition, whose members had flocked to the polls to vote for the former actor. For the first four years of the epidemic, Reagan refused to even utter the word "AIDS." The Reagan-appointed director of the CDC, Dr. James O. Mason complained of having to discuss various forms sexual activity with total strangers (Shilts 1987). Whether the negligence was due to distaste or malice, NIH spending on AIDS was drastically inadequate. In 1982, NIH expenditure for research into Toxic Shock Syndrome equaled $36,100 per death, and that for Legionaire's disease was $34,841 per death. In fiscal 1982, the NIH expenditure per AIDS death was a mere $8,991 (Shilts 1987).

In 1983, the San Francisco Board of Supervisors allocated $2.1 million for AIDS programs. Coupled with the $1 million from the previous year, San Francisco's spending on AIDS "exceeded the funds released to the entire country by the NIH for extramural AIDS research" (Shilts 1987, p. 186). Half of the money was allotted to establish the world's first AIDS clinic at San Francisco's General Hospital, which opened in July 1983.

With no drugs specific to treat HIV, and few available to treat the opportunistic infections that accompanied the resultant immune failure, AIDS patients were desperate. A significant number of the early AIDS-infected population included men who had pioneered the gay rights movement. This was a politically sophisticated group that already had a large activist infrastructure in place when the epidemic appeared. Almost overnight, gay rights activists became AIDS activists, fighting not for equality but for existence. Pressure was brought to bear on the government through protests, marches and demonstra-

tions. A powerful activist group emerged, AIDS Coalition to Unleash Power! (ACT UP) which spread across the country and later, across the globe.

Many members of the gay AIDS population were also well educated and traveled, and used these privileges to their advantage. AIDS patients began researching promising treatments, unapproved by the FDA, but available overseas or across borders, where drug approval and distribution is less stringently regulated. Patients traveled to Mexico and other countries to buy the illicit medications and smuggle them back to the USA, frequently employing techniques developed by marijuana traffickers. In 1987 the first "buyer's clubs" were established in San Francisco and New York City, where they functioned as underground pharmacies for smuggled treatments and alternative therapies such as vitamins and herbs (Arno 1992).

In order to find some effective drug against HIV, the National Cancer Institute (NCI) began soliciting the profit-minded pharmaceutical corporations for compounds for federally funded testing. In 1985 a compound, azidothymidine (AZT), showed some evidence of anti-HIV activity in the laboratory. Responding to pressure from activists and the public-at-large the FDA accelerated the rigorous 3-phase testing requirements and allowed AZT to be widely distributed upon initial evidence of clinical benefit (Arno 1992). For some patients, AZT was effective with manageable side effects. Others were plagued by intolerable headaches, loss of appetite, stomach upset, stomach pain and nausea or vomiting.

One of the primary killers of AIDS patients was a wasting syndrome that resulted from a number of illness-linked influences including oral thrush, anorexia and chronic diarrhea. Wasting is defined as the loss of more than 10% of baseline bodyweight (Bayer 2000). The fact that, for many, AZT further suppressed the appetite and frequently resulted in gastric distress was a dire situation for patients who were already wasting due to the primary disease (Richman et al.1987).

Although AZT was rushed to approval, it proved to be no magic bullet. At best it extended survival by months, slowing viral replication, but not eradicating it (Bayer 2000). It was a cruel irony that the side effects of the only approved antiviral drug for HIV mimicked and aggravated some of the most devastating symptoms of the illness. In order to be effective, the drug had to be taken on a regular schedule, at very frequent intervals through the day and night. This meant that the side effects never had an opportunity to subside. With constantly depressed appetites it was a challenge for PWA's (People with AIDS) on AZT to ingest enough calories to rebuild body mass. Patients affirmed that marijuana usage not only eased and abated the gastrointestinal distress from both illness and remedy, but induced a voracious hunger and a seemingly insatiable compulsion to eat, known as "the munchies." For many

AIDS patients, smoking or eating cannabis became a primary component of their unorthodox treatment arsenal.

In 1983, the first call from an AIDS patient extolling marijuana's benefits reached Robert Randall, founder of the Alliance for Cannabis Therapeutics (ACT). Randall, a glaucoma patient whose suit against federal agencies forced the establishment of the Compassionate Investigational New Drug program for marijuana, had devoted his life to promoting medical marijuana and working to make it a prescription drug. ACT was founded as a nonprofit organization to further this endeavor.

Randall's most successful campaign had been an effort to persuade state legislatures to pass legislation to protect medical marijuana users (primarily cancer and glaucoma patients) from arrest and prosecution. By 1983, 34 states had enacted legislation that made marijuana available though "research programs." Because of marijuana's classification as a Schedule I drug, with the presumption of no recognized medical benefits and a high abuse potential, it could only be distributed for research through the National Institute on Drug Abuse (NIDA). Thus, Randall and the other legal users were provided with marijuana through the IND research exemption, despite the fact that no data was collected. Similarly, the states could only obtain cannabis by enacting specific research programs.

Production of the cannabis for federally approved research was conducted at a 5-acre farm at the University of Mississippi under a contract with NIDA (Randall 1998). The growing demand for marijuana from states with established research programs vastly outpaced the cannabis farm's ability to supply the drug. California alone requested 1 million marijuana cigarettes from NIDA (Randall 1998). In order to meet the needs of the state programs a new production plan would have to be established with state-of-the-art production techniques. Rather than move in this direction, FDA officials turned to synthetic THC as a surrogate for whole cannabis.

A stable method for the delivery of synthesized delta-9-tetrahydrocannabinoid, or THC in sesame oil, was developed for research purposes in the 1970's (Rosenkrantz et al. 1972). Later research established that oral THC had antiemetic properties and was significantly better than a placebo in reducing vomiting caused by chemotherapeutic agents (Sallan, Zinberg and Frei 1975). Despite the clinical evidence of antiemetic activity for oral THC, the researchers suggested that smoking might be a preferable route of administration due to its more reliable absorption compared to gastrointestinal ingestion. Moreover, smoking provides greater opportunity for individual patient control by permitting the patient to regulate and maintain the "high" (Sallan, Zinberg and Frei 1975). Efforts to prepare an aerosol delivery system for THC failed due to (Olsen et al. 1976, p. 86), "excessive tack of the spray and hence poor transport to the lungs."

Despite the irregular absorption and unpredictable mental effects of oral THC, it was the only solution available to stem the push for medical marijuana from the states. On June 26, 1980, an FDA advisory panel rushed to approve, by just one vote, the distribution of synthetic THC pills to oncology patients through a NCI research program (Washington Post 1981, p. A1). Panel member Dr. Charles G. Moertel, director of clinical cancer research at the Mayo Clinic, criticized the action and decried (Washington Post 1981, p. A1), "the current political hysteria for the general release of THC. I wonder if perhaps the weight of this political pressure does not exceed the scientific evidence justifying release." Robert Randall protested the diversion from cannabis to THC, charging that (Washington Post 1981, p. A1), "federal agencies are using their control of the nation's legal marijuana supply to corrupt the intent of the state laws." Only six of 34 states with research laws managed to obtain actual marijuana cigarettes (Randall 1998; Musty and Rossi 2001). The rest of the states were provided with "marijuana capsules," which were actually oral THC pills.

The resulting studies with THC evidenced some anti-emetic activity and the studies with inhaled cannabis found it to be safe and effective against chemotherapy-induced nausea (Randall 1998). With evidence that THC was effective against nausea in hand, the FDA faced the challenge of bringing it to market as a prescription drug. NIDA's chief of research and technology, Robert Willette noted that (Tucker 1979, p. 33), "Since THC isn't patentable, it's going to take a lot of coercion by the government to get a pharmaceutical company to market THC."

The FDA found a distributor for the THC pills in Unimed, a small New Jersey-based company that had no prescription drugs on the market, just over-the-counter remedies, and was eager to expand. After clearing the FDA-approval procedures, THC was given the generic name, dronabinol and marketed as Marinol . THC in the form of dronabinol was moved from a Schedule I to a Schedule II designation, alongside cocaine and morphine, which permitted distribution by prescription in June of 1985. Despite the fact that a synthesized and concentrated version of cannabis' most active compound was rescheduled, the source plant was not. With marijuana withheld, and synthetic THC available by prescription, the state medical marijuana research programs slipped into dormancy.

Along with leading the state movements for medical marijuana, Robert Randall, through ACT, was working for Congressional legislation to move marijuana into the Schedule II designation. Although a bill attracted a broad coalition of supporters, it never moved out of committee.

ACT was also a co-petitioner with NORML (National Organization for the Reform of Marijuana Laws) for public hearings into rescheduling marijuana. After years of litigation against the Drug Enforcement Administration (DEA) in pursuit of these hearings, they were held in front of the DEA's Administra-

tive Law Judge, Francis Young in 1987 and 1988. Judge Young ruled that marijuana has “an acceptable medical use in treatment in the United States” and proclaimed that the Schedule I classification was “unreasonable, arbitrary, and capricious” (Young 1998, p. 68). On December 30, 1989, DEA Administrator Jack Lawn announced his rejection of Judge Young’s directive to reschedule.

Between the time of Judge Young’s decision and Administrator Lawn’s rejection of it, Robert Randall received a call from an AIDS patient in Texas who had reversed his wasting condition with marijuana, but was now facing jail after being arrested for possession. The patient, Steve L. wanted to gain admission into the Compassionate IND Program. Steve’s physician agreed to sponsor him and after months of wrangling with evasive agencies, he was approved. The shipment of NIDA joints reached Steve on January 25, 1990, just 18 days before he died (Randall 1991; Randall 1998). Randall wrote an obituary for Steve that ran in *High Times*, a magazine for marijuana users. At the end of the tribute was included the phone number for ACT’s offices.

In Panama City, Florida, a young couple was in desperate trouble. Kenny and Barbra Jenks were slipping into the late stages of AIDS. They were impoverished, with few health care resources and had just been arrested by the local narcotics task force and charged with serious felony violations: manufacturing marijuana with intent to distribute. Whittled away to near-skeletal thinness by HIV, the Jenks had been urged to smoke marijuana at an AIDS-support group meeting. After the meeting, they had been slipped a joint, but being “straight arrows” were reluctant to try it. When they eventually did try the marijuana, they discovered the munchies and both began to regain some weight and vitality. The couple became regular users of small amounts of cannabis, but without reliable connections within the “drug culture” or black market they often went without their medicine. Rather than rely on chance, Kenny planted some seeds and had cultivated two short and scraggly plants when they were arrested.

Kenny Jenks, a hemophiliac, had contracted HIV through the clotting factor he took to prevent death from internal bleeding. Barbra, Kenny’s high school sweetheart, had contracted the virus from him. When their trailer was raided and agents found the tubing and syringes used for infusing clotting factor, Kenny was accused of being a heroin addict who was growing cannabis to support his habit.

Out on bail, Kenny came across the issue of *High Times* with Steve L.’s obituary and called ACT. Upon hearing the Jenks’ story, Randall endeavored to find them legal representation and improved medical care from an AIDS expert who was willing to sponsor their IND application (Randall 1991).

Randall quickly realized the Jenkses’ public relations value for promoting the use of marijuana for AIDS patients. They were literally “Ken and Barbi wholesome”: salt-of-the-earth, heterosexual, monogamous. They lacked the

homosexual and IV-drug use baggage that right-wing opponents could seize on to distort the issue by discomforting Middle America.

In March of 1991, after Kenny and Barbra had endured the standard institutional delays and had their IND supplies in hand, they joined Randall for a press conference to announce the launch of a new ACT endeavor, Marijuana/Aids Research Service (MARS). The service of the organization was to provide AIDS patients and their doctors with a uniform template with which to apply to the FDA for a Compassionate Use IND. Randall explained (Randall 1998, pp. 359-360), "Prior to MARS, physicians who requested IND forms from the FDA could wait for weeks, even months for the forms. When the papers did arrive there was no explanation about how to complete the 31 questions . . . Physicians who once struggled for hours to answer arcane FDA questions, could sit with an AIDS patient, open a MARS packet, go through a checklist and put an application in the mail in under an hour." The MARS forms were promoted by the Jenks and distributed to AIDS organizations throughout the country.

The AIDS-patient population responded enthusiastically to MARS. Many gay men who comprised the bulk of the AIDS-infected population had a profound distrust of the culture of authority and had never believed the "reefer madness" propaganda. These were largely children of the "Woodstock Nation." They had smoked pot, dropped acid, demonstrated against the war in Vietnam, gleefully violated anti-sodomy laws, and marched for gay liberation. There was little or no stigma associated with cannabis use for these patients, and they were eager for any remedy that worked. Soon, dozens of Compassionate Use IND applications began arriving at the FDA.

In June of 1991, just 3 months after the launch of the MARS effort, the patients receiving Compassionate Use IND marijuana found that their monthly shipments of the drug had been interrupted. The reason for the withholding of the marijuana became clear on June 21 when Dr. James O. Mason, Chief of the US Public Health Service (PHS) and former director of the Centers for Disease Control (CDC), announced the closure of the Compassionate Use IND Program saying (Isikoff 1991, p. A14), "If it's perceived that the Public Health Service is going around giving marijuana to folks, there would be a perception that this stuff can't be so bad. It gives a bad signal . . . there's not a shred of evidence that smoking marijuana assists a person with AIDS." Mason, much as his good friend and booster, Utah Senator Orrin Hatch, was infused with a pious attitude of abstention and priggishness. As director of the CDC, confronting the expanding AIDS crisis, Mason (Shilts 1987, p. 399), "couldn't bring himself to utter the word 'gay' when he met a gay delegation during his first day on the job." In justifying his decision to close the program, Mason expressed concern that AIDS patients taking medical marijuana (Isikoff 1991, p. WH 19), "might be less likely to practice safe behavior."

In response to Mason's abrupt announcement, Robert Randall organized a media blitz that highlighted the patients who were IND cannabis recipients in order to illustrate the political and callous nature of the decision. The well-oiled AIDS activism machinery engaged over the medical marijuana issue and phone trees were activated. The PHS, FDA, DEA and the White House Office of National Drug Control Policy (ONDCP) were clogged with calls from desperate patients, confused loved ones and angry activists. The AIDS-activist group, ACT UP, led a medical marijuana protest in the form of a "die-in" which closed the headquarters of Health and Human Services (HHS). Randall recalled (Randall 1998, p. 380), "what the agencies did not anticipate was the onslaught of public anger . . . This aggressive telephonic battering had a profoundly corrosive effect on institutional morale."

Mason's sudden and unilateral decision for IND closure had cast the ONDCP in a particularly bad light and put the agency in an untenable situation. Less than two months prior to Mason's announcement, ONDCP Assistant Director Herb Kleeber had appeared on the NBC television network's *TODAY* show to caution the ill away from buying cannabis on the black market. Kleeber reassured patients that (Today 1991, p. 25), "no one's been turned down in the last two years. There are over 35 such IND's on the market currently and the waiting period usually is less than one month . . . They can get an exception from the FDA. That's the way to go rather than go out and break the law."

Mason's announcement made Kleeber and the ONDCP seem foolish at best and dishonest at worst. The White House drug policy staff seemed moved and disturbed by the desperation of the calls they received, and initiated a challenge to the Compassionate Use IND's termination. The resulting interagency battle forced the PHS to suspend the closure until the conflict could be resolved.

Mason had planned to completely end the program, forcing Randall, the Jenks and other IND recipients to switch to dronabinol, despite the absence of any clinical data showing it to be safe and effective for their diseases. The ONDCP staff, in contrast, felt that this approach was a duplicitous betrayal of trust. They wanted NIDA to continue providing marijuana to all of those approved to use it, including those who had never received their supplies. In a scolding letter to Mason, Ingrid A. C. Kolb, acting deputy director for demand reduction at the ONDCP, wrote (Ostrow 1992, p. A13), "For HHS to treat this matter as just another bureaucratic decision is unconscionable and, to me, shows an intolerable lack of compassion." With the conflict at a stalemate, the final decision was passed up to HHS Secretary Louis Sullivan. In March of 1992, Sullivan settled the issue with a compromise. The program would close, but the current recipients would receive marijuana for the rest of their lives or until cured. The approved but unsupplied patients, primarily people with

AIDS, were prescribed dronabinol in lieu of cannabis. For HHS, the fix was in and the issue was settled. But no one could explain how someone with nausea and vomiting was supposed to hold down a pill the size of a bath oil bead.

While Randall and the Jenks were promoting MARS, a grassroots medical marijuana movement was germinating in San Francisco. On the same day that Steve L. became the first AIDS patient to receive legal marijuana (Randall 1991), career cannabis dealer and gay activist Dennis Peron's home was raided by San Francisco narcotics officers. Peron operated a marijuana market in the predominantly gay Castro neighborhood and the bulk of his clients were HIV-positive. During the raid, Peron and his housemates, one of whom was in the late stages of AIDS, were physically and psychologically abused by being hogtied, threatened with weapons and taunted with homophobic and AIDS-phobic slurs. The only cannabis tied to Peron was a moderate amount of top-grade marijuana that he and his ill housemate, Jonathan smoked. Peron went free when he and Jonathan explained to the court that the marijuana was an effective medicine against wasting. Two weeks after the trial, Jonathan succumbed to his disease and Peron (1996) recalled, "I kept thinking about how I was going to get even and I kept thinking that every AIDS patient needs pot and that is where I got the idea for a club." Peron knew that if he could openly sell cannabis, with medical use as a justification and a shield, then he would be tormenting and humiliating the narcotics squad while helping the ill.

Peron's first step was to gather enough voters' signatures to qualify a "Hemp Medications" proposition for San Francisco's November ballot. The proposition (Prop P 1996, p. 1) advised "the state of California and the California Medical Association to restore hemp medicinal preparations to the list of available medicines in California."

Peron's timing was perfect. Coincidentally, Prop P qualified for the ballot just days before James Mason announced the Compassionate IND closure and benefited enormously from the resulting publicity and furor over the lack of cannabis for AIDS patients. San Francisco was playing David to the federal government's Goliath, and the local press loved it.

In November, Prop P passed with an impressive 78% of San Francisco's voters saying yes to medical marijuana. Peron celebrated the victory by opening a "cannabis buyer's club" based on the model of the Healing Alternatives Buyer's Club which had sold unapproved medicines to AIDS patients for years without harassment. And since jurors are taken from the voter registration rolls, Peron felt sure that 78% of any jury would vote to acquit him should trouble arise. Peron's clientele grew as word of his operation spread, with some patients and caregivers traveling in from out of state to buy a variety of cannabis products in a safe and clean environment.

When HHS Secretary Sullivan finalized the Compassionate Use IND's closure in early 1992, San Francisco County Supervisor Terence Hallinan initi-

ated an effort inspired by Prop P, to protect local medical marijuana users from being arrested (Hallinan 1998).

At San Francisco General Hospital's Ward 86, the AIDS ward, an increasing number of patients were reporting benefits from using cannabis. The ward's "Volunteer of the Year" for two years running, "Brownie Mary" Rathbun, had earned her nickname by baking marijuana-laced brownies for her "kids with AIDS." In June, 70-year-old Brownie Mary was arrested in the process of baking a large batch of illegal confections. After admitting that she baked the brownies and drove them to San Francisco to give them to AIDS and cancer patients, Brownie Mary was arrested and charged with transporting marijuana, a felony. The arrest of a little old lady for baking marijuana brownies for AIDS patients was the ultimate human interest story and was beamed around the globe by CNN. Rathbun was defiant, vowing (San Francisco Examiner 1992, p. A6), "My kids need this and I'm ready to go to jail for my principles . . . I'm not going to cut any deals with them. If I go to jail, I go to jail."

Dr. Donald Abrams, Assistant Director of the AIDS Program at San Francisco General Hospital, was in Amsterdam attending the International AIDS Conference when he retired to his hotel room, turned on the television and saw the story of Volunteer of the Year, Brownie Mary's arrest.

Also watching as the Brownie Mary saga unfolded was Rick Doblin, founder of the Multidisciplinary Association for Psychedelic Studies (MAPS) which worked to facilitate clinical research into the therapeutic potential of Schedule I drugs. Seeing that Brownie Mary was a volunteer at the world's premier AIDS facility, Doblin sent a letter to the program suggesting that a clinical trial of cannabis as a treatment for AIDS wasting should be conducted at "Brownie Mary's institution" (Abrams 1995). The letter was forwarded to Dr. Donald Abrams who pioneered and directed community-based clinical trials for HIV through San Francisco General Hospital's Community Consortium.

Community-based clinical trials became a third avenue of drug approval, along with federally initiated trials and research by pharmaceutical companies. Doctors treating AIDS patients became researchers, providing the opportunity for the collection and assessment of clinical data. The first drug approved through community-based research was inhaled pentamadine for *Pneumocytis carinii*. Pentamadine had originally been given intravenously, but it was toxic to the kidneys and other organs. Inhaled, the drug was delivered directly to the lungs where it was needed, sparing the rest of the body from some degree of side effects. Therefore, the idea of an inhaled medicine was not anathema to Abrams.

Abrams had also witnessed patients and friends with AIDS using cannabis and seeming to benefit from it. He had seen no serious harm, as with alcohol or cigarettes, or any number of prescription drugs at his disposal. With so many

patients using medical marijuana it seemed as though some data should be gathered in case there was some unknown harm. There were rampant assertions and assumptions that marijuana could further damage the immune system.

Abrams contacted Doblin, and collaboration began to design a protocol for a study of cannabis to treat the AIDS-wasting syndrome. Abrams and Doblin consulted with FDA researchers in designing the trial and ushered it through approval from hospital committees, state and university investigational review boards and the FDA. Efforts to move forward with the research, which would have compared control patients with patients taking dronabinol and patients smoking marijuana, hit a roadblock at NIDA. In order to conduct the trial, Abrams needed marijuana, which only NIDA could supply.

While Abrams and Doblin worked on obtaining cannabis for the study, the San Francisco Board of Supervisors passed a measure to designate medical marijuana use as the lowest police priority. They also declared "Brownie Mary Day" in San Francisco. Rathbun's charges were subsequently dropped in Sonoma County, and she became a local folk hero.

The passage of Prop P and the supporting resolution inspired other communities to take similar actions. As support for medical marijuana grew, so did its use. Dennis Peron moved his buyer's club from a studio apartment to a large former dance studio at one of the city's primary public transportation hubs and he invited the media in to see. Buyer's clubs began appearing in other locations, including New York, Seattle, and Key West.

More initiatives passed and the overwhelming public support for medical marijuana motivated California State legislators to pass a measure that would reclassify cannabis as a Schedule II drug available by prescription. Governor Pete Wilson vetoed the bill, appropriately noting that state law could not make a drug available by prescription.

At San Francisco General Hospital, Abrams was waiting for approval from NIDA of his request for a supply of cannabis for the AIDS-wasting study. For 9 months, Abrams queried NIDA officials about the status of his request and was stymied with assurances and apologies. In April of 1995, Alan Leshner, Ph.D., Director of NIDA informed Abrams that (Leshner 1995), "we cannot comply with your request." Leshner complained that (CNN 1996), "The study was flawed and I couldn't justify using our scarce resources . . . "

Abrams was infuriated and responded with a scathing letter. Abrams (1995) wrote:

> To receive the first communication from your office nine months after we sent the initial submission is offensive and insulting . . . The apparent absence of any possibility to discuss your concerns and to modify the protocol so that we may work together for the benefit of our patients is also unacceptable in my opinion . . . your concerns about the scientific

> merit of the study have not been shared by a number of competent reviewers and investigators.

Abrams closed the letter with a blistering attack:

> Finally the "sincerity" with which you share my "hope that new treatments will be found swiftly" feels so hypocritical that it makes me cringe . . . You had an opportunity to do a service to the community of people living with AIDS. You and your Institute failed. In the words of the AIDS activist community: SHAME!

At this point in the history of the medical marijuana movement a confluence of political deception, scientific frustration and grassroots activism generated a dynamic synergy for reform. Activists used Leshner's rejection and Abrams' response as public relations weapons.

Shortly after NIDA's rejection of the AIDS study the California legislature passed a bill to exempt medical users from prosecution under state law. Governor Wilson also vetoed this bill, and passed the buck saying (San Francisco Chronicle 1995, p. A22), "the Clinton Administration said in August marijuana should not be used for any purpose," referring to Attorney General Janet Reno's refusal to call a moratorium on the arrest of medical users.

Dennis Peron's Cannabis Buyer's Club had grown to accommodate over 10,000 members and relocated to a vast 5-story building in the heart of downtown San Francisco (Peron 1996). It was from this location that a network of activists, patients and suppliers launched a ballot initiative to enact a law to protect medical marijuana users from state anti-marijuana laws. Simultaneously, Donald Abrams and his research team were retooling their clinical trial to obviate any claims from NIDA that it "lacks scientific merit."

California's ballot initiative process allows citizens to enact or repeal laws that legislators have failed to address satisfactorily. In the fall of 1995, California activists began gathering signatures to qualify a medical marijuana proposition for the 1996 election. The effort succeeded following an infusion of cash from a group of wealthy sympathizers and the campaign for Prop 215 began.

Alan Leshner was in a difficult position as director of NIDA. The legislation that established the Institute charged the agency to (NIDA 1972, p. 55), "develop and conduct comprehensive health education, training, research, and planning programs for the prevention and treatment of drug abuse and for the rehabilitation of drug abusers." By definition, NIDA was precluded from facilitating research into the benefits of illicit drugs. If Leshner had violated the mission statement of his Institute, he could face a spate of political assault aimed at embarrassing the Clinton Administration.

Rather than continue to take the heat of public displeasure, Leshner washed his hands of the responsibility and agreed to provide marijuana for any study that passed NIH peer review, a part of the funding process for govern-

ment-sponsored research. Abrams and the THC study team believed that this would work to neutralize political considerations.

In August, just three months before Californians would vote on Prop 215, Abrams received a rejection notice from the NIH. When the peer review panel's comments arrived Abrams began to see how deeply the political reefer madness bias had penetrated. Abrams (1998, p. 166) wrote:

> Two of the three reviewers mentioned in their comments that they were unclear as to why the Consortium investigators would chose to conduct a trial with such a "toxic" substance. The final reviewer was concerned that if patients with AIDS wasting developed increased appetite following marijuana ingestion . . . that they may subsequently develop hyperlipidemia (high cholesterol and triglycerides) and atherosclerosis. The peer review panel seemed to have missed the point: the reason the substance was being studied was because it was being so widely used in the local community. The reviewers apparent lack of insight into the natural history of the HIV-wasting syndrome also was of concern to the once again defeated protocol team.

The rejection of the second proposed study of marijuana use by AIDS patients came at a time when federal mouthpieces, most notably Drug Czar Barry McCaffrey, were trying to make a strong case against Prop 215, and a similar but broader measure in Arizona, by claiming that (Russel 1996, p. A8), "There is not a shred of scientific evidence that shows that smoked marijuana is useful or needed. This is a cruel hoax that sounds more like something out of a Cheech and Chong show." The retired general's argument lacked authority, especially when countered with a world class researcher's complaint that (Kanigal 1996, p. C1), "The government is saying there are no scientific studies proving the medicinal benefits of marijuana, but they're also not letting studies be conducted."

On Election Day, 56 percent of California's voters said "yes" to medical marijuana. It was a decisive victory that was a powerful indictment of the government's unwillingness to deal honestly with the issue. Arizona's more sweeping measure, allowing for the medical use of all Schedule I drugs, passed with 65 percent of the vote. Rather than heeding the will of the voters and redirecting their efforts toward dealing with medical marijuana scientifically, federal authorities moved to squash the uprising. McCaffrey and other opponents insulted voters by saying that they were "asleep at the switch" or were duped by pro-drug millionaires. When this technique failed to illicit a *mea culpa* from the voting public, Attorney General Janet Reno, supported by HHS Secretary Shalala, McCaffrey, and Leshner, threatened that "U.S. Attorneys in both states will continue to review cases for prosecution and DEA officials will re-

view cases for prosecution and DEA officials will review cases, as they have, to determine whether to revoke the registration of any physician who recommends or prescribes so-called Schedule I substances" and that doctors might face "further enforcement action" (CNN 1996). The grim and punitive nature of the press conference clearly illuminated the federal government's brutal indifference to the plight of medical marijuana users. The outcry against the announcement was swift, massive and seething. The public, physicians and their professional organizations were outraged. Editorials across the nation decried the action as an interference with the doctor-patient relationship. A group of San Francisco doctors and patients responded by filing a class action suit against Reno, McCaffrey and DEA Administrator Thomas Constantine for violating the First Amendment to the Constitution.

The eruption of anger was so profound that within a week McCaffrey had retreated from his "not a shred of evidence" soundbite and announced a $1 million review of scientific evidence on marijuana as medicine to be conducted by the National Academy of Science's Institute of Medicine. The NIH also rushed to conduct a 2-day workshop on medical marijuana that continued to invalidate the drug czar's "Cheech and Chong" rhetoric. Rick Doblin, who attended the workshop and was still promoting Abrams' efforts to conduct research assured him that (Doblin 1997), "NIDA, NIH, and the Clinton Administration will have a very difficult time convincing the press that the publicly announced new openness to research is more than a PR front and delay tactic if your next NIH grant gets rejected."

A month earlier, in January, Abrams had met with Leshner at NIDA and discussed the barriers to researching marijuana's benefits. Leshner emphasized to Abrams that the Institute was "the National Institute *on* Drug Abuse, not *for* Drug Abuse" (Abrams 1997). Consequently, Abrams and the marijuana team devised a study to assess the potential harm that marijuana or dronabinol might cause by interfering with the new AIDS drugs, protease inhibitors. The study also included examination of weight gain and other measures that could indicate if there was a therapeutic benefit of cannabis for the subjects.

This third submission by Abrams' team was given special attention in the reviewing process and was promptly approved. On May 12, 1998, the first patients were enrolled in the study and began a 21-day stay at San Francisco General Hospital, during which they were randomized to dronabinol, a dronabinol placebo, or 3.95% THC cannabis in the form of NIDA's cigarettes. Initial results of the study were presented at the XIII International AIDS Conference in South Africa. Early findings indicate that: "Cannabinoids, smoked or oral, do not adversely effect HIV RNA levels after 21 days exposure. Smoked marijuana and dronabinol lead to significant increases in caloric intake and weight" (Abrams 2000). The THC Study Team also suggested that, "Future trials

should investigate the effectiveness of marijuana in: appetite stimulation/ weight gain, nausea, pain" (Abrams 2000). The long-sought research has made a significant contribution to validating the "anecdotal" claims of the tens of thousands of AIDS patients who have used cannabis medicinally. The publication of more detailed findings from the study is pending.

The government's "new openness to research" did not dissuade the public of the notion that federal agencies had placed politics before science. Eventually, medical marijuana initiatives similar to Prop 215 were passed by voters in Arizona, Oregon, Washington, Maine, Nevada, Alaska, and the District of Columbia. In Hawaii, the state legislatures defied federal policy by passing a medical marijuana bill.

When the $1 million IOM report was released in March of 1999, it cautiously affirmed the medical use of marijuana, suggesting that better methods of delivery than smoking be devised.

And although research is proceeding slowly, it is finally underway. NIDA relaxed its restrictions requiring NIH peer review for all medical marijuana research, but added a PHS review panel process before providing medical marijuana to researchers. Several studies are pending in California through a state-funded research program including investigations into marijuana for multiple sclerosis and peripheral neuropathy.

Currently, as evidenced by the success of state ballot propositions, the American general public has generally accepted the idea that cannabis is a safe and effective medicine. The experiences of desperate AIDS patients using medical marijuana helped to change the nation's perceptions of the drug from menace to medicine.

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Marijuana Use in HIV-Positive and AIDS Patients: Results of an Anonymous Mail Survey

Stephen Sidney

SUMMARY. While there is a great deal of anecdotal reporting regarding the medical use of marijuana in HIV-positive patients, there have been few systematic surveys performed. The prevalence of medical use of marijuana in HIV-positive and AIDS patients was assessed by an anonymous mail survey of 1970 attendees of HIV clinics in the San Francisco, Oakland, and South Sacramento medical centers of the Kaiser Permanente Medical Care Program (KPMCP) in California. Of 442 responders (22.4% response rate), 147 (33.3%) reported current use of marijuana for medical purposes. Among current users, the most common reasons for using cannabis were: to feel better mentally/reduce stress (79%), improve appetite/gain weight (67%) and decrease nausea (66%). Patterns of use were heterogeneous, with daily use of cannabis reported by 34% of current users. Nearly half of participants reported buyers' clubs as a source for obtaining cannabis, a finding of particular interest because of recent successful government efforts in closing down these clubs in California. In combination with other reported surveys, these data suggest that the use of marijuana for medical purposes is relatively common in HIV-positive and AIDS patients.

Stephen Sidney, MD, is affiliated with Kaiser Permanente Medical Care Program, Oakland, CA.

Address correspondence to: Dr. Sidney, Division of Research, 3505 Broadway, Oakland, CA 94611 (E-mail: sxs@dor.kaiser.org).

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INTRODUCTION

The medical use of marijuana has become a highly political issue in the United States, with several states having passed initiatives approving its use for this purpose in the face of prohibition of its use for any purpose by federal law. Cannabis has specifically been advocated as a therapeutic adjunct to ameliorate the nausea and loss of appetite commonly associated with the wasting syndrome in AIDS (Grinspoon and Bakalar 1993). Media reports estimated that in 1996 up to 11,000 San Francisco Bay Area residents with HIV infection or AIDS were utilizing cannabis buyers' clubs to obtain marijuana for medical use (Abrams 1998).

While there are many anecdotal reports regarding the use of marijuana in HIV-infected individuals, there are few data available on its prevalence in this population. In order to provide information regarding this important issue, we conducted an anonymous mail survey of HIV-infected patients in 3 medical centers of the Kaiser Permanente Medical Care Program in Northern California to determine the prevalence of medical marijuana use and information regarding reasons for use, frequency of use, and sources. We report here the findings of this survey.

METHODS

The study population was composed of the attendees of HIV clinics in the San Francisco, Oakland, and South Sacramento medical centers of the Kaiser Permanente Medical Care Program, a prepaid medical care program which provides medical care to over 25% of the population of the greater San Francisco Bay area. In order to comply with the legal and administrative concerns of Kaiser Permanente, we performed an anonymous survey, i.e., no identifying information was included on the questionnaire. The initial mailing was sent to San Francisco members in January 1998. Because of a low response rate to the initial mailing of a 6-page questionnaire (about 10%), we developed an abbreviated 4-page questionnaire containing key questions from the longer questionnaire and re-mailed it in a subsequent newsletter in May, 1998, thanking those who had responded and requesting questionnaire completion from those who had not. Oakland members also were mailed the 6-page questionnaire with a flyer from the clinic in May 1998, with a later mailing of the 4-page questionnaire in July 1998. South Sacramento members were sent only the 4-page questionnaire in August 1998. A total of 1,970 members were sent questionnaires (1,200 from San Francisco, 650 from Oakland, and 120 from

South Sacramento). A postpaid return envelope was provided for the questionnaires.

The questionnaire was mostly composed of check-off responses (yes/no, or choices of categorical responses). Data from the questionnaire responses were entered and processed into a SAS data set. A section was provided at the end of the questionnaire for participants to voluntarily provide identification information and to indicate whether we could have permission to review their medical records in the next year to determine if they had experienced medical complications from AIDS, and if they were interested in being notified about other research projects in the future. The questionnaire and survey procedures were approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

RESULTS

A total of 458 questionnaires were returned. Voluntary self-identification was provided on 158 questionnaires from the San Francisco and Oakland centers, of which 16 represented duplicate responses, i.e., responses to both the initial and follow-up mailing. For these 16 responders (including 10 current users of marijuana for medical purposes), the initial questionnaire was included and the follow-up questionnaire excluded. This left 442 questionnaires (22.4% response rate) for the analysis, of which 229 were from San Francisco, 166 from Oakland, and 47 from South Sacramento. AIDS diagnosis was reported by 50% of responders, with 48% of the responders HIV positive without AIDS (2% unknown). Current use of cannabis for HIV or AIDS was reported by 147 patients (33.3%; 147/442), with 276 patients (62.4%) reporting that they did not employ it (19 [4.3%] unknown). The prevalence of current cannabis use was slightly higher for AIDS patients (35.7%) than for HIV-infected patients without AIDS (30.5%). The responses to several questions regarding use in current users are shown in Table 1. The most commonly reported reason for using cannabis from the 5 specific reasons listed on the questionnaire was to feel better mentally/reduce stress (79%), followed by improve appetite/gain weight (67%) and decrease nausea (66%). One-half of the patients did not know whether their doctor approved of their use of marijuana; of the remainder, 85% (63 of 74) reported that their doctor approved of their use of marijuana. The predominant mode of ingestion of cannabis was smoking (95%). Daily use was reported by 34% of current users, with 7% reporting use of less than once per week. About one-half of users reported use of cannabis once per day (49%), with 12% reporting use more than 3 times per day. The most common sources for obtaining cannabis were buying from a friend or someone you know (59%) and purchasing from a buyers' club (48%), with

TABLE 1. Responses of Current Users of Marijuana for Medical Purposes (N = 147) to Several Questions About Use

Question	Percent
Main reason(s) for using marijuana	
Feel better mentally	79
Improve appetite/gain weight	67
Decrease nausea	66
Decrease pain/discomfort	48
Decrease symptoms of other medications	39
Does your doctor approve of your use of marijuana?	
Yes	43
No	6
Don't know	50
Missing	1
Method(s) of marijuana ingestion used (current users)	
Smoking	95
Eating	20
Capsule	3
Days of marijuana use per week	
< 1	7
1-3	33
4-6	26
7	34
missing	1
Number of times marijuana used per day	
1	49
2-3	35
> 3	12
Missing	4
Current source(s) for obtaining marijuana	
Buy from a friend or someone you know	59
Buyers' club	48
Grow my own	16
Buy from someone you don't know	9
Other	1

16% reporting growing their own. The money currently spent per month for marijuana ranged from $0 to $500, with a median monthly cost of $80. Of the 55 current cannabis users who reported ever using Marinol , nearly all (98% [54 of 55]) reported that cannabis provided better relief of their symptoms; the other reported identical relief from both marijuana and Marinol.

In order to estimate the potential effect of duplicate form completion by San Francisco and Oakland survey participants on the prevalence of current use, we applied the duplicate form completion (i.e., completion of both initial and follow-up questionnaires by the same participant) rate for self-identified survey participants and the prevalence of current marijuana users among responders who completed forms in duplicate to the "anonymous" questionnaires, i.e., questionnaires from participants who did not self-identify. Using these data, of the 253 "anonymous" questionnaires from San Francisco and Oakland, 26 would be duplicates (253 × 10.1%) including those of 16 current users (26 × 62.5%). This would result in a current use prevalence estimate of 31.5% (131/416), slightly lower that the 33.3% estimate noted earlier.

DISCUSSION

The current study is larger than any that have been published regarding medical marijuana use in HIV-positive and AIDS patients. While the interpretation of the results of this survey must be tempered by the low response rate, the 33% prevalence of medical marijuana use in HIV-positive patients is comparable to that found in the few other published surveys. Wesner (1996) reported that 36.9% of a sample of 123 patients in Honolulu with HIV-positive status or AIDS responding to a mailed questionnaire survey responded that they had used cannabis as therapy. One-quarter of 228 HIV sero-positive men in the Sydney Men and Sexual Health study reported therapeutic use of cannabis (Prestage, Kippax and Grulich 1996). Thirty-two percent (32%) of 72 patients at a clinic in Alabama reported current use of cannabis (Dansak 1997).

The data regarding frequency of use are of interest because they demonstrated a heterogeneous pattern. Daily users were in the minority, and 40% of the responders indicated use on 3 or fewer days per week. On days of use, about half the current users reported using cannabis only once per day. In a survey of 102 HIV-positive clients of buyers' clubs in San Francisco and Oakland, more frequent use was reported compared to the Kaiser Permanente survey, with 26% of patients reporting cannabis use 3 times per day compared with the 12% in the Kaiser Permanente survey reporting use of at least 3 times per days (Child, Mitchell and Abrams 1998). In the Alabama study, 17% (4 of 23) patients who were current cannabis users reported using in 6 to 10 times weekly with all others reporting less frequent use (Dansak 1997). The other

surveys noted earlier did not provide data regarding the patterns of cannabis use in HIV-infected patients.

The data regarding the sources for obtaining cannabis are of particular interest because of the high prevalence of buyers' club use. Buyers' clubs achieved increased popularity in California after the passage of Proposition 215 in 1996 legalizing the medical use of marijuana, but most have been closed down subsequent to the passage of this measure as a result of federal enforcement efforts.

The major limitation of the study is the low response rate, resulting from the requirement for anonymous mailing and the resultant inability to directly contact non-responders in order to increase the response rate. Because of the anonymity requirements, we were also unable to perform comparisons of the characteristics of responders and non-responders. As noted in the results, it is likely that some individuals who did not identify themselves completed both the initial and follow-up questionnaire, but that the impact of this on the estimate of the prevalence of the current use of marijuana would be minimal.

In summary, a substantial proportion (33%) of the HIV-infected patients who responded to this survey reported the current use of cannabis as a medical treatment for a variety of symptoms. The patterns of use were heterogeneous. The results of this survey, in combination with other surveys that have been reported, suggest that the use of marijuana for medical purposes is relatively common in HIV-positive and AIDS patients.

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Differential Effects of Medical Marijuana Based on Strain and Route of Administration: A Three-Year Observational Study

Valerie Leveroni Corral

SUMMARY. Cannabis displays substantial effectiveness for a variety of medical symptoms. Seventy-seven patients took part in a study in California to assess the efficacy of organically grown *Cannabis sativa* and *indica* strains in treatment of various medical conditions via smoking or ingestion. HIV/AIDS was the most frequent condition reported, at 51%. Standardized rating forms provided 1892 records that were statistically analyzed. Results demonstrated that in the case of nausea and spasm, symptom expressions are definitely affected by various methods of cannabis administration. However, while *Cannabis indica* strains increased energy and appetite, it is useful to note that in treating nausea in HIV/AIDS and orthopedic diagnosis groups, *Cannabis sativa* and *C. indica* strains proved equivalent. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Cannabis, medical marijuana, *Cannabis sativa, Cannabis indica*, AIDS, HIV

Valerie Leveroni Corral is affiliated with Wo/Men's Alliance for Medical Marijuana, 309 Cedar Street #39, Santa Cruz, CA 95060, a collective of patients and caregivers, creating community, building hope, dissolving barriers, providing support and free medical marijuana since 1993. *www.wamm.org* (E-mail: info@wamm.org).

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INTRODUCTION

Marijuana, whether *Cannabis sativa* or *Cannabis indica*, produces its medical and other effects by virtue of the concentration and balance of various active ingredients, especially the cannabinoids, which are unique to marijuana, but also including a wide range of terpenoids and flavonoids. Terpenoids are cannabis constituents that provide the characteristic strong odor of marijuana and hashish. Flavonoids are any of the flavone derivatives. The concentration and relative proportions of these ingredients depend on the plant's genetic structure and applied hybridization techniques, and as such, allow for a substantially varied outcome.

Little is known about how differences in constituent profiles translate into differences in therapeutic effectiveness. A range of effects has been ascribed to THC (tetrahydrocannabinol is the primary psychoactive component of marijuana) and CBD (cannabidiol, a compound related to THC) when administered in purified form. Studies are lacking on the differential clinical effects produced when varying "menus" of constituents are taken together.

Another factor bearing on the effects and the effectiveness of marijuana is the route of administration. Orally administered marijuana is absorbed more slowly than when delivered systemically (e.g., smoking, vaporizers). Moreover, the liver metabolizes orally ingested marijuana to produce a potent and long-acting cannabinoid (11-hydroxy-THC), which induces varied reactions in medical marijuana patients and is often not well tolerated. However, once more, there is little information available concerning the differential clinical effects of oral vs. smoked forms of marijuana.

A major obstacle to obtaining data concerning differential clinical effects is, of course, the illegality of medical marijuana use. Almost equally troublesome, however, is the widespread view that medical knowledge can be gained only through randomized controlled trials. It is becoming increasingly accepted that valid causal inferences can be, and frequently are drawn quite regularly in medicine without such studies. As such, observational studies are quite capable of generating useful information, provided due care is taken to keep careful track of the process. In this case, careful and consistent documentation would be required concerning: (1) which forms of marijuana are being taken and by what route, and (2) what outcome is experienced by patients.

The passage of Proposition 215 in California in 1996 legalized medical marijuana under state law, thus clearing some legal obstacles to research. Prior to the passage of Proposition 215, two or more cannabis buyers' clubs and our collective comprised of patients and caregivers were in operation. Several provider associations have been operating since that time despite harassment of some by law enforcement agencies.

Valerie Leveroni Corral founded the Wo/Men's Alliance for Medical Marijuana (WAMM) in 1993. WAMM is a collective of patients and caregivers attempting to create community, build hope, dissolve barriers, and provide support and medical marijuana at no cost to patient members who possess a signed and verified recommendation from a physician licensed to practice medicine in California. A genetically-monitored, organic, communal garden is tended by WAMM client/ participants under the direction of Mike Corral and Valerie A. Leveroni Corral.

A primary function in this community based educational system is the creation of a database of information regarding the treatment of different symptoms with distinct cannabis varieties. This is achieved through daily effectiveness surveys and statistical analysis (Appendix, Tables 17 and 18). Our present collection of data also includes measures of effectiveness of cannabis on autoimmune illnesses, such as systemic lupus erythematosis, as well the many other disorders, including muscular dystrophy, epilepsy, quadriplegia, paraplegia, Parkinson's disease, glaucoma, arthritis, fibromyalgia, depression and migraine. However, AIDS and HIV-related conditions are the most frequently represented among our clientele.

WAMM initiated a study in 1993 designed to address the question of differential clinical effects between *Cannabis sativa* and *C. indica* strains and hybrids, and also examining effects of inhaled and ingested routes of administration. This study is ongoing and now includes "blind" trials where the varieties used are not apparent to the participating patient. A statistician generated all presented analyses.

MATERIALS AND METHODS

The determination of the variety of cannabis was based on the country of origin of the seeds strains and physical characteristics of each plant variety. We assure the genetic purity through carefully controlled breeding techniques, substantiated by twenty-five years of experience in cultivation and propagation of cannabis. Personal interaction took place with patient use of cannabis in more than one hundred different terminal cases.

An assessment instrument form is provided weekly to participating patients (see Tables 17 and 18). The patient places a label from a weekly supply on the seven day form, denoting the variety and form of cannabis (inhaled or ingested), the number of "puffs" if inhaled medicine is used and the amount or weight employed. All participants were instructed in a specific method of inhaling. Patients were requested to use and denote dosages correlated to the relief of specific symptoms. Participants observed and rated symptoms before and after cannabis use to assess their severity. This was done upon rising from

sleep in all cases except "insomnia" and prior to using any cannabis. Assessments were made weekly, at minimum, or as much as seven times per week, in order to assess effectiveness and of different strains upon different target symptoms.

Findings were derived from data gathered during the time period of June of 1993 into early 1997. Statistical analysis consisted of frequency analysis, paired T-tests of "before" and "after" scores on each measured symptom or condition, and a series of one-way ANOVAs on route of administration (either inhaled or ingested), cannabis strain, and diagnosis.

Because the therapeutic effects of cannabis are sometimes ascribed to its mood-altering effects, we also performed a correlation analysis of the change in mood score with other outcome variables.

Inhalation methods of cannabis consisted mostly of smoking, with some use of vaporization, although patient reports of effectiveness appear substantially lessened when this technique was employed. This could certainly depend on the quality of the vaporizer design.

Ingested forms of cannabis consisted of baked goods and "mother's milk" (a soymilk-based liquid), and a whole cannabis tincture made with pure grain alcohol with leaf or a combined blend of leaf and flowers. Strains of marijuana were *C. sativa* and *C. indica* and their hybrids. The morphological distinction between these strains was determined by experienced cannabis cultivators associated with WAMM, based on characteristic features of the two sub-species, varieties or strains.

These sub-species varied from week to week and included the following pure strains and hybrid strains: *C. sativa*, *C. indica*, as well as hybrids of both, being the identified female *C. sativa* × male *C. indica*, as well as the identified female *C. indica* × male *C. sativa*. We secured a method of analysis of the chemical content of test materials, although we believe that the findings may be subject to error. Results from a drug detection laboratory indicated that *C. sativa* measured: THC 23.7%, CBD < 0.1% and CBN < 0.1%. Results indicated that *C. indica* strains measured: THC 19.6%, CBD < 0.2% and CBN < 0.5%. Cannabis potency testing results by ElSohly Labs of the same sample of *C. sativa* after storage for eight months yielded a value of THC 17.6%.

RESULTS

Seventy-seven patients completed a total of 1892 forms (range 1-256, median 8) during the three-year study period. Of these, 43 were male (56 percent), 22 were female (29 percent) and 12 were not coded as to gender. The distribution of primary diagnoses is presented in Table 1.

Thirty-nine patients (51 percent) had HIV/AIDS; 14 (18 percent) had neurological diseases, and 7 (9 percent) had a principle diagnosis of cancer.

To avoid biasing results due to a large proportion of questionnaires being completed by relatively few patients, we standardized the analysis by reviewing a maximum of eight records per patient, the median number completed by study subjects. These records were randomly chosen. Accordingly, our analysis contained 432 records. Of these, 261 (61 percent) referred to *C. sativa* experiences; 65 (15 percent) were *C. indica*, while 105 (24 percent) were coded "other." Certain types of marijuana were donated or undeclared, we labeled these as "other" and included them in our findings. Ingested forms were also recorded (Table 4). Some entries were coded with missing information, entered as slang or incorrectly named; these were excluded.

Paired t-tests of before and after health status revealed that the following symptoms were relieved to a statistically significant extent by therapeutic cannabis (without regard to strain or route of administration): pain, energy, mood, nausea, appetite, and awareness. The remaining symptoms were not reliably relieved to the same extent. Table 5 and Table 6 show the scores on each variable. The magnitude of improvement was unrelated to clinical diagnosis, as determined in ANOVA (Table 10), with one exception: the degree of relief of nausea was greater in the HIV/AIDS group (4.54 units) than in the orthopedic group (1.58 units) to a statistically significant extent ($p = 0.04$).

We next performed ANOVA on the strain of marijuana ingested: *C. sativa* and *C. indica*. The mean change scores, "before" scores minus "after" scores for patients with each condition, were calculated. For the most part, some observed changes were unrelated to strain of marijuana. However, two symptoms, energy and appetite, were improved to a statistically greater extent by *C. indica* than by either *C. sativa* or "other."

C. indica produced a mean improvement in energy of 3.76 units (vs. 1.53 for *C. sativa* and 2.22 for "other") and a mean improvement in appetite by 5.22 units (vs. 3.41 for *C. sativa* and 4.32 for *C. indica*). These differences were significant at the 0.012 and 0.005 levels, respectively (Table 8).

ANOVA was then conducted using route of administration as the independent variable (Tables 6 and 7). For the most part, ingested and inhaled marijuana had similar magnitudes of effects. Only one symptom, spasm, showed preferential improvement using smoked over ingested marijuana ($p = .036$) (Table 6). Patients reporting "other" routes of administration had substantially less relief of nausea than patients inhaling or ingesting marijuana (Table 7).

It is reported that THC may reduce spasms associated with both neurological and non-neurological disorders (Hollister, 1986; British Medical Association Report, 1997). It is interesting to note that the non-psychoactive cannabinoid cannabidiol has been shown to exhibit anticonvulsant properties in certain animal studies. In the case of some patients it has been noted to reduce or prevent

the onset of both spasms and seizures when used alone or as an adjunct medicine. It appears that there are receptor sites for cannabinoids that have beneficial effects on seizure activity.

Finally, analysis of the Pearson correlation coefficients between changes in mood scores and changes in other symptom scores revealed only a single statistically significant correlation, between mood and energy level ($p = 0.035$). Mood was not correlated with any other outcomes, including pain relief ($p = 0.817$) (Table 11).

DISCUSSION

We analyzed 432 records of therapeutic cannabis exposures, including information on strain (*C. sativa, C. indica*, or other), and route of administration (inhaled, ingested or other). The outcome variables consisted of scores to a series of questions on symptoms, completed by the patient both before and after administering cannabis medicines.

Results indicate that cannabis was uniformly effective in relieving symptoms across a wide range of diagnostic categories. No differences were observed in the extent to which symptoms were relieved based on diagnosis, except that patients with HIV/AIDS experienced more relief of nausea than patients with primary orthopedic diagnoses (Table 13).

On several occasions, terminally ill patients remarked upon a recurrent phenomenon, described as a "shift in consciousness" or "perception" allowing them to approach their impending death more "openly" or in a more "relaxed" manner. This is of particular interest, as each patient also reported a reduction in anxiety often associated with the dying process. Future studies will further examine measures anxiety in the cannabis patient population.

C. *indica* appeared to be superior to *C. sativa* and "other" in improving energy and appetite (Table 9). Otherwise, no differences in strain effects were observed. Route of administration had little effect on outcome in our series. Two symptoms, spasm (Table 6) and nausea (Table 7) showed preferential improvement with smoking as compared to ingestion. In no condition was the ingested route superior to smoking for symptom management.

Changes in mood were not correlated with changes in other outcomes except for a modest correlation with energy (Table 11). The finding that mood did not correlate with other outcomes casts doubt on the theory that therapeutic cannabis effects are related primarily to improvement in mood. Conversely, this may pertain with the notion suggested by some patients that mood is not necessarily correlated to the concept of "feeling better." In our findings, it appeared that mood was often independent of symptom expression. This result is interesting because it appears in written testimony by patients in their surveys that they believe

changes in awareness or consciousness do affect overall healing. We plan to further examine the validity of these phenomena in future studies.

These findings support that few differences were noted by patients between *C. sativa* and *C. indica* strains and between ingestion vs. inhaled routes of administration. This is likely due to modest observed differences in cannabinoid content in the supplied strains. We hope that a reliable and accessible means of analysis will become available in the near future to further assess these hypotheses.

This study is limited by the lack of blinding. For this reason, in 1998 a revised protocol was instituted in which patients receive a one-week supply of therapeutic cannabis at a time without knowledge of particular variety provided. Patients continued completing forms on a weekly basis. This method of blinding is expected to provide a more rigorous test of any distinctions between *C. sativa* and *C. indica* strains. Results may have implications for subsequent crossbreeding of strains to maximize therapeutic effects.

This study is only a small first step in the attempt to develop improved cannabis medicines for affected patients. The most significant current limitation to this type of research is the absence of a convenient legal mechanism in the USA for analyzing cannabis samples for biochemical constituent content. Until this limitation is overcome, progress in this area will be slow at best.

On the other hand, we should not underestimate the value of clinical observation in judging cannabis strains and their differential clinical effects irrespective of chemical content. Thus, while the work we report here does not definitively address issues of chemical variability, we believe that our findings provide at the very least a good working hypothesis for use in future studies.

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APPENDIX

Purpose of the Project

- To determine if there are physical, mood and perception changes resulting from use of the test article.
- To determine if the method of delivery affects measures of effectiveness.
- To determine if different types of cannabis affect diagnoses and measures of effectiveness.
- To assess the correlation between changes in mood and other measures of effectiveness.

Summary of Population

N = 77
43 males (56%)
22 females (29%)
12 missing gender distinction (15%)

TABLE 1. Description of Population by Primary Diagnosis

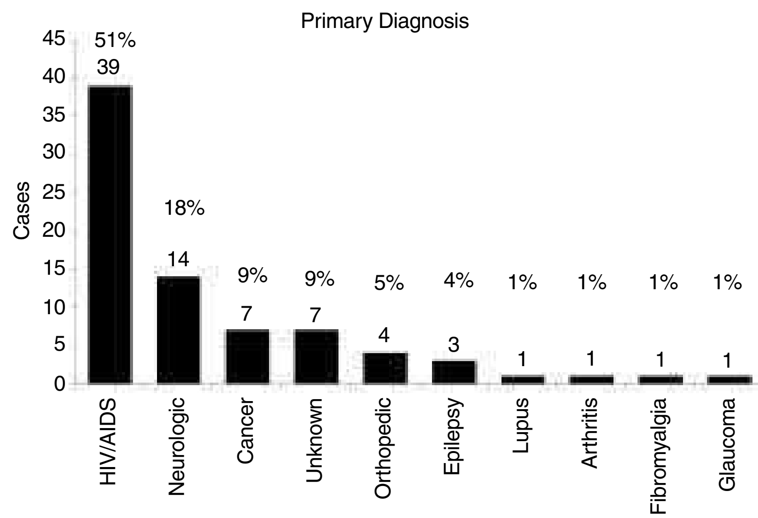

TABLE 2. Description of Patient Population by Secondary Diagnosis

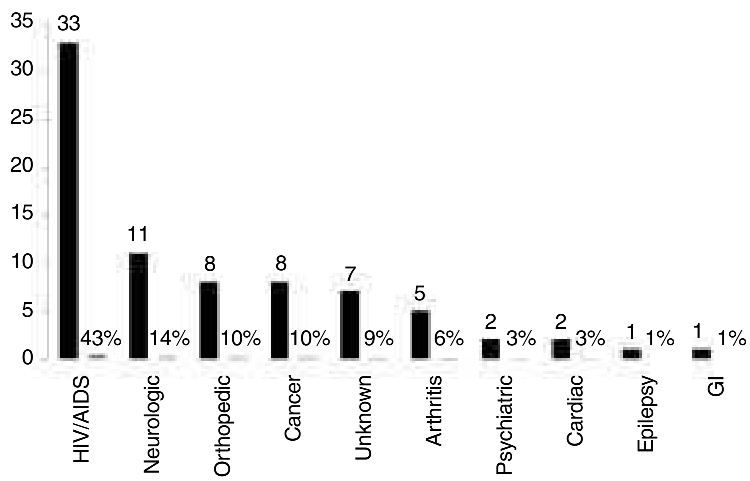

TABLE 3. Questionnaire Structure Measures of Effectiveness

Variable	None	Most	Desired Effect
Pain	1	10	Decrease
Energy	1	10	Increase
Mood	1	10	Increase
Nausea	1	10	Decrease
Appetite	1	10	Increase
Muscle Spasms	1	10	Decrease
Seizures	1	10	Decrease
Ocular	1	10	Decrease
Insomnia	1	10	Decrease
Awareness	1	10	Increase
Neuropathy	1	10	Decrease

Questionnaire Logistics

- 1892 Questionnaires Completed over 3 years
  Range of 1 to 256 questionnaires
  Average of 8 questionnaires/patient
  Analysis completed based on the average number of questionnaires completed (to normalize data for analysis)

TABLE 4

Statistical Methods

- 432 questionnaires analyzed
- Frequency analysis, Paired t-tests, Paired t-test correlations, One Way ANOVA, Post-Hoc (Bonferroni), Pearson Correlation and Multivariate tests performed
- One Way ANOVA conducted on variables using the following 3 groups
- Group 1–test article “ingested”
  - Muffins
  - Mothers milk
- Group 2–test article “inhaled”
  - African Queen
  - Purple Indica
- Group 3–“Other”
- One Way ANOVA performed on the following test article groups:
  - Sativa (261–61%)
  - Other (105–24%)
  - Indica (65–5%)
- Multivariate Tests performed for type of Cannabis, diagnosis, and change in variable
  - Pillai’s Trace
  - Wilks’ Lambda, and
  - Tests of Between-Subjects Effects
- One Way ANOVA, Bonferroni, Post-Hoc tests performed for definition of diagnosis and treatment effectiveness

All tests performed using SPSS (Statistical Program for Social Scientists) Version 9.0

TABLE 5

Question One

- Are there physical, mood and perception changes resulting from use of the test article?

Paired Samples t test

- Comparing means before and after
  - 95% confidence interval (2-tailed)

Variable	***Before***	***After***	***Difference***	
Pain	6.98	3.26	−3.72	3
Energy	4.12	6.04	1.92	3
Mood	4.30	7.32	3.02	4
Nausea	7.06	2.78	−4.28	3
Appetite	3.02	6.96	3.94	4
Awareness	5.73	6.97	1.24	3

All are significant

TABLE 6

Question Two

- Does change in variable vary by method of treatment: ingested, inhaled or other?

Question Two–Means of Variable Changes by Mode of Consumption

	1	2	3	p
Pain	−3.75	−3.45	−3.67	0.274
Energy	2.05	1.14	1.18	0.630
Mood	2.98	2.54	3.81	0.840
Nausea	−4.39	−4.50	−2.22	0.934
Appetite	4.05	2.94	3.28	0.418
Spasm	−3.42	−3.95	−3.60	0.008*
Seizure	−0.14	N/A	−4.75	0.177
Ocular	−2.63	−2.54	−2.86	0.099
Insomnia	−3.88	−3.44	−4.28	0.036*
Awareness	1.31	−0.41	1.72	0.259

*Significant

ANOVA
Question Two

Examination of the mean change (One way Anova–95% confidence interval)
Significance was found for the following variables
Spasm $p = 0.008$
Insomnia $p = 0.036$

TABLE 7

Interpretation of ANOVA Method of Test Article Delivery

- Group 1 is different than group 3.
- Average group 1 (ingested) = −4.39.
- Average group 2 (inhaled) = −4.50.
- Average group 3 (other) = −2.20.
- There is greater improvement in nausea (0.36) with ingestables vs. “other.”
- Ingestables and inhaled groups are not different.

TABLE 8

Question Three

- Are changes in variables related to the different types of cannabis and primary diagnoses?

Mean Change of Variables in Treatment Test Article Groups

	Other	Sativa	Indica	p
Pain	−3.49	−3.99	−2.93	0.078
Energy	2.22	1.53	3.06	0.012*
Mood	2.94	2.89	3.76	0.327
Nausea	−4.67	−4.19	−4.01	0.470
Appetite	4.32	3.41	5.22	0.005*
Spasm	−4.33	−3.53	−2.23	0.071
Seizure	−0.67	−2.12	0.50	0.316
Ocular	−3.27	−2.34	−3.00	0.646
Insomnia	−4.53	−3.82	−3.18	0.221
Awareness	1.75	0.96	1.24	0.173

One Way Anova–95% CI
*Significant

TABLE 9

Interpretation of ANOVA Method of Test Article Treatment Group

- The Indica Group is different than Sativa Group
  - Average Indica = 3.06
  - Average Sativa = 1.53
  - Average Other = 2.22
- There is greater improvement in energy (0.012) with Indica vs. Sativa and "Other."
- Sativa and Other treatment groups are not different.

Interpretation of ANOVA Treatment Group

- Indica was more effective to increase energy and appetite in any primary diagnosis group.
- Use of any test article was effective in treating Nausea in the Orthopedic and HIV/AIDS diagnosis group.

TABLE 10

Mean Change in Variable by Primary Diagnosis

	Ortho	Neuro	AIDS	Other	Cancer	p
Mood	4.36	4.05	2.87	1.33	2.64	0.001*
Pain	−4.93	−4.02	−3.31	−3.90	−3.27	0.011*
Energy	3.54	1.33	2.31	1.07	1.23	0.017*
Mood	4.36	4.05	2.86	1.33	2.64	0.094
Nausea	−1.58	−4.21	−4.54	−3.97	−4.18	0.015*
Appetite	4.57	3.50	4.44	3.08	3.00	0.010*
Spasm	−4.17	−4.05	−1.83	−3.29	−4.91	0.401
Seizures	NA	−1.86	−0.89	NA	NA	0.001**
Ocular	NA	−2.91	−2.00	−4.00	NA	0.334
Insomnia	−4.68	−4.66	−3.49	−2.93	−5.08	0.000*
Awareness	2.21	1.07	1.15	0.65	2.25	0.000*

One Way Anova 95% CI
*Significant
**Small sample size unable to correlate

TABLE 11

Interpretation of ANOVA Method for Primary Diagnostic Group

- The Orthopedic and Neurological group are different than the “Other” primary diagnostic group.
- There is greater improvement in Mood ($p = 0.008$) for the Orthopedic group vs. “Other.”
- There is greater improvement in Mood ($p = 0.001$) for the Neurological group vs. “Other.”

Average Orthopedic	4.36
Average Neurological	4.04
Average HIV/AIDS	2.87
Average “Other”	1.33
Average Cancer	2.64

- There is no difference between the AID/HIV and Cancer groups.

TABLE 12

Interpretation of ANOVA Method for Primary Diagnostic Group

- The Orthopedic group is different than the “Other” primary diagnostic group.
- There is greater improvement in Energy ($p = 0.43$) for the Orthopedic group than “Other.”

Average Orthopedic	3.54
Average Neurological	1.33
Average HIV/AIDS	2.31
Average “Other”	1.07
Average Cancer	1.23

- There is no difference between the Neurological, AID/HIV, and Cancer groups.

TABLE 13

Interpretation of ANOVA Method for Primary Diagnostic Group

- The HIV/AIDS group is different than the Orthopedic primary diagnostic group.
- There is greater improvement in Nausea (p = 0.04) for the HIV/AIDS group than Orthopedic primary diagnostic group.

Average Orthopedic	−1.58
Average Neurological	−4.21
Average HIV/AIDS	−4.54
Average "Other"	−3.97
Average Cancer	−4.18

- There is no difference between the Neurological, Other, and Cancer groups.

TABLE 14

Interpretation of ANOVA Method for Primary Diagnostic Group

- There is improvement in Appetite (0.010) for all diagnostic groups.
- There is no difference in mean change for the Appetite variable for specific primary diagnostic groups.

Average Orthopedic	4.57
Average Neurological	3.50
Average HIV/AIDS	4.44
Average "Other"	3.08
Average Cancer	3.00

TABLE 15

Interpretation of ANOVA Method for Primary Diagnostic Group

- There is improvement in Insomnia (p = 0.000) for all diagnostic groups.
- There is no difference in mean change for the Insomnia variable for specific primary diagnostic groups.

Average Orthopedic	−4.68
Average Neurological	−4.66
Average HIV/AIDS	−3.49
Average "Other"	−2.93
Average Cancer	−5.08

TABLE 16

Interpretation of ANOVA Method for Primary Diagnostic Group

- There is improvement in Awareness (p = 0.000) for all diagnostic groups.
- There is no difference in mean change for Awareness specific to primary diagnostic groups.

Average Orthopedic	2.21
Average Neurological	1.07
Average HIV/AIDS	1.15
Average "Other"	0.65
Average Cancer	2.25

Correlation Analysis Question Four

- Is change in mood correlated to change in energy?
  p = .035*
- Is change in mood correlated to change in pain?
  p = .817
- Is change in mood correlated to change in nausea?
  p = .434
- Is change in mood correlated to change in insomnia?
  p = .647
- Is change in mood correlated to change in awareness?
  p = .073

*Significant

Conclusions

- There were observed changes in pain, energy, nausea, appetite, and awareness variables from the use of the test article.

TABLE 17

WAMM MEDICAL MARIJUANA EFFECTIVENESS SURVEY

Please read the instructions on the other side of this page.

Name or ID: (Use your WAMM ID number if concerned about privacy. You may place the label from your medicine here.)	**Gender**	**Age**	**Race**	**Diagnosis**	**Years since diagnosis**

Weekly Medicine Allotment

Buds	Muffins	Milk	Brownies	Other

DAY:	WEDNESDAY		THURSDAY		FRIDAY		SATURDAY		SUNDAY		MONDAY		TUESDAY	
DATE:														
MEDICINE TYPE:														
DOSAGE UNIT:														
DOSAGE:														
CONDITION\N	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Appeptite														
Awareness														
Consciousness														
Enegy														
Insomnia														
Libido														
Mood														
Nausea														
Neuropathy														
Ocular pressure														
Pain														
Seizures														
Spasms														

TABLE 18

Comments: (Use additional sheets of paper as needed. We are very interested in your comments.)

Instructions

Each day of the week, fill in the information BEFORE you take your medication for the first time in the day, and then again AFTER you take your medication for the first time of the day. Using a scale of 1 to 10, with **1 meaning WORST and 10 meaning BEST**, mark how you are feeling in the spaces provided. If the condition (symptom) improves, the number goes up.

Notice that the week begins on Wednesday in order to synchronize with our weekly meetings on Tuesdays.

If a condition does not apply to you, simply leave it blank.

Make sure to fill in at least one date.

Terminology

Appetite	Desire for food or drink	Medicine type	The code that appears on your medicine container or medicine name such as milk, muffins, brownies, buds.
Awareness		Mood	State or quality of feeling at a particular time. Prevailing emotional tone or general attitude
Best	Subjective experience of highest quality	Nausea	Sickness at the stomach, especially when accompanied by a loathing for food and an involuntary impulse to vomit.
Consciousness		Neuropathy	Symptoms of a diseased nervous system like tingly sensations.
Diagnosis	Name of disease such as cancer, HIV, glaucoma	Ocular pressure	Pressure within the eye
Dosage	Number of dosage units	Pain	Physical suffering or distress
Dosage unit	Name of dose, such as puffs, ounces, grams, bites, drops, fraction of weekly allotment (for example 1/7 means 1/7 of the weekly allotment.	Seizures	A sudden attack, as of epilepsy or some other disease
Energy	Capacity for vigorous activity	Spasms	Sudden, abnormal, involuntary muscular contraction
Gender	Male, female, transgendered	Worst	Subjective experience of lowest quality
Insomnia	Inability to sleep		
Libido	Sexual instinct or drive		

Developed by Rick Sinatra

Marijuana and Cannabinoids: Effects on Infections, Immunity, and AIDS

Guy A. Cabral

SUMMARY. Marijuana and its major psychoactive component, delta-9-tetrahydrocannabinol (THC), alter resistance to bacterial, protozoan, and viral infections *in vivo* and *in vitro*. These alterations have been accompanied by modifications in functional components of the immune system. In addition, marijuana and THC, as well as other cannabinoids, have been reported to directly affect functional activities of lymphocytes, macrophages, natural killer cells, and other immunocytes. These include effects on cytokine production resulting in a shift in the balance of Th1 versus Th2 cytokines. Both receptor and non-receptor mediated modes of action have been proposed as causative of cannabinoid effects. Reports that marijuana and THC alter anti-microbial activity *in vivo* and *in vitro* indicate that its use presents a potential risk of decreased resistance to infections. However, few controlled longitudinal epidemiological and immunological studies have been undertaken to correlate the immunosuppressive effects of marijuana smoke or cannabinoids on the incidence of infections or disease in humans. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

Guy A. Cabral, PhD, is affiliated with the Department of Microbiology & Immunology, Medical College of Virginia Campus of Virginia Commonwealth University, Richmond, VA 23298-0678.

Address correspondence to: Guy A. Cabral, PhD, Department of Microbiology & Immunology, Virginia Commonwealth University, Medical College of Virginia Campus, 1101 East Marshall Street, Richmond, VA 23298-0678 (E-mail: gacabral@hsc.vcu.edu).

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KEYWORDS. AIDS, HIV, cannabinoid receptors, cannabinoids, delta-9-tetrahydrocannabinol, immunity, infections, marijuana, THC

INTRODUCTION

Marijuana, *Cannabis sativa*, is a highly complex substance that contains in excess of 400 chemical entities. Among these is a group of compounds classified as cannabinoids of which some of its 66 or more members exert a variety of effects on cells of the immune system. The cannabinoid that has been linked to the majority of the immunosuppressive effects attributable to marijuana is delta-9-tetrahydrocannabinol (THC), its major psychoactive component. Studies using *in vitro* and *in vivo* experimental models have indicated that marijuana or THC affects cell-mediated immunity (Klykken et al. 1977; Smith et al. 1978), humoral immunity (Mishkin and Cabral 1985), and cellular defenses against infectious agents (reviewed in: Cabral and Dove Pettit 1998; Friedman and Klein 1999). Compromised resistance in mice, rats, and guinea pigs to infection with amebae (Burnette-Curley et al. 1993), herpes simplex virus (Morahan et al. 1979; Mishkin and Cabral 1985; Cabral et al. 1986a; Cabral et al. 1986b; Fischer-Stenger et al. 1992), Friend Leukemia virus (Specter et al. 1991), *Listeria monocytogenes* (Morahan et al. 1979), *Staphylococcus aureus* (Baldwin 1997), *Treponema pallidum*, and *Legionella pneumophila* (Klein et al., 1993; Klein et al. 1994; Newton et al. 1994) has been reported. Although there are numerous reports relating to the deleterious effects of THC, this cannabinoid also has been reported to have therapeutic potential (Munson and Fehr 1983; Dewey 1986). It exhibits anti-nociceptive properties, has the ability to reduce intraocular pressure and bronchial constriction, and acts as an anti-convulsant and anti-emetic agent. Major advances have been made in the pharmacology and molecular biology of cannabinoids, the cell biology of endogenous systems, and the expression of cognate receptors. High-affinity and low-affinity cannabinoid ligands, non-cannabinoid ligands, and receptor subtype-specific antagonists have been developed. In addition, cannabinoid receptor subtype-specific molecular probes and antibodies as well as knockout animals have become available in the last few years. These experimental tools should prove highly useful to basic scientists and clinical researchers as they assess the acute as well as long-term effects of marijuana and cannabinoids on the immune system.

EFFECTS OF CANNABINOIDS ON INFECTIONS

Other than a few early studies on host resistance in mice or guinea pigs to infections with herpes simplex viruses and *Listeria monocytogenes*, there have

been few studies of the effects of cannabinoids on infectious diseases. Experimental evidence which links directly the use of cannabis or cannabinoids in a recreational or therapeutic mode to compromised host resistance in humans is not available. Data obtained have been extrapolated from studies performed on experimental animals or using *in vitro* culture systems.

Arata et al. (1992) reported that THC affects macrophage functional activities *in vitro* against *Legionella pneumophila*, the causative agent of Legionnaires' disease. Treatment of macrophages from A/J mice with THC resulted in enhanced growth of *Legionella* within macrophages. In addition, THC treatment overcame macrophage restriction of the growth of *Legionella* that is normally induced by macrophage activation with bacterial lipopolysaccharide. Klein et al. (1994) extended these studies to demonstrate that THC induces significantly increased mortality in mice infected with *Legionella*. *Legionella*-primed mice challenged with a secondary lethal dose survived the challenge infection. However, significantly increased mortality was obtained in animals subjected to the same *Legionella* infection and challenge regimen but receiving THC three weeks prior to the *Legionella* exposure. Kusher et al. (1994) assessed the effect of THC on the synthesis of tumor necrosis factor alpha (TNF) by human large granular lymphocytes (LGL) in culture. These investigators reported that THC at physiological levels down-regulated TNF production and diminished LGL cytolytic activity against K562 tumor cells. Based on these studies, it was suggested that, since the NK/polymorphonuclear neutrophil axis represents an important early defense against the opportunistic fungus *Candida albicans,* repression of this system by THC could contribute to susceptibility to infections with opportunistic pathogens.

The few studies performed to assess the effects of marijuana or cannabinoids on resistance to infection in humans have yielded contradictory results. Gross et al. (1991) reported that marijuana consumption altered responsiveness of human papillomavirus (HPV) to systemic recombinant interferon alpha 2a treatment. Simeon et al. (1996) examined characteristics of Jamaicans who smoked marijuana before sex and their risk status for sexually transmitted diseases. The results of a national sample of 2580 randomly selected individuals administered a questionnaire indicated that more persons who smoked marijuana before sex had a history of sexually transmitted diseases than non-marijuana smokers. The difference was significant among men, but not among women. The investigators indicated that, although it was not possible to establish whether the association was causal, there was an increased risk for sexually transmitted diseases among men who smoked marijuana before sex.

On the other hand, Miller and Goodridge (2000) undertook a retrospective study to evaluate the relationship between marijuana use and sexually transmitted diseases in pregnant women. Examination of clinical records over a twelve and one-half month period of 86 women entering prenatal care, and

who used no illicit substance other than marijuana, was compared with that of 441 drug-free women. No significant differences in the prevalence of gonorrhea, chlamydia, syphilis, human immunodeficiency virus, hepatitis B virus, human papilloma virus, or herpes virus were noted. Also, no differences were found for prevalence of more than one infectious agent. It was concluded that marijuana use was not associated with sexually transmitted disease in pregnant women.

In contrast to the equivocal results obtained for marijuana and susceptibility to infections, Bass et al. (1996) indicated that a synthetic non-psychotropic cannabinoid could prove useful in the treatment of bacterial infection. The synthetic non-psychotropic cannabinoid dexanabinol (HU-211), when used in combination with antimicrobial therapy, was effective in reducing brain damage in a rat model of pneumococcal meningitis. Brain edema and blood-brain barrier impairment were significantly reduced for infected animals receiving combination ceftriaxone and HU-211 therapy as compared with control animal groups.

EFFECTS OF CANNABINOIDS ON IMMUNE CELLS

Effects of cannabis and cannabinoids on host resistance to infections have occurred in association with changes in cellular and humoral immunity, suggesting a functional linkage between these two events. Studies conducted since the early 1970s reported that cannabinoids and marijuana affect the functions of various immune cells from rodents and humans including B lymphocytes (Zimmerman et al. 1977; Smith et al. 1978; Baczynsky and Zimmerman 1983; Klein and Friedman 1990; Nahas and Osserman 1991; Kaminski et al. 1992), T lymphocytes (Nahas et al. 1974; Gupta et al. 1974; Peterson et al. 1976; Nahas et al. 1977; Klein et al. 1985; Cabral et al. 1987; Klein et al. 1991; Lee et al.1995), macrophages (Mann et al. 1971; Drath et al. 1979; Lopez-Cepero et al. 1986; Cabral and Mishkin 1989; Burstein et al. 1994), and natural killer (NK) cells (Specter et al. 1986; Patel et al. 1985; Klein et al. 1987; Kawakami et al. 1988).

Cannabinoids may affect the immune system by altering functional capabilities of immunocytes rather than affecting their relative numbers or distribution. Del Arco et al. (2000) exposed Wistar rats to the potent synthetic cannabinoid agonist HU-210 during gestation and lactation. It was found that perinatal exposure partially affected the distribution of lymphocyte subpopulations in the spleen and peripheral blood. HU-210 treatment resulted in a reduction of T-helper cells in the spleen and in a dose-related decrease in the ratio of T-helper/T-cytotoxic lymphocytes in peripheral blood. In addition, animals exhibited decreased responsiveness of the hypothalamic-pituitary-adre-

nal (HPA) axis. Basal levels of luteinizing hormone (LH) were elevated in animals receiving HU-210 while those for corticosterone were reduced. The investigators concluded that maternal exposure to cannabinoids resulted in minor changes in the development of the immune system, but could induce long-lasting alterations in the functional status of the HPA axis.

Baldwin et al. (1997) evaluated the function of human alveolar macrophages recovered from the lungs of nonsmokers and habitual smokers of tobacco, marijuana, or crack cocaine. Macrophages recovered from marijuana smokers were deficient in their ability to phagocytose *Staphylococcus aureus*, and were severely limited in the capacity to kill bacteria and tumor cells. Experiments in which NG-monomethyl-L-arginine monoacetate, an inhibitor of nitric oxide synthase, was used suggested that macrophages from marijuana smokers were not able to use nitric oxide (NO) as an antibacterial effector molecule. Furthermore, macrophages from marijuana smokers, but not from smokers of tobacco or cocaine, produced lower levels of TNF , granulocyte/macrophage colony-stimulating factor (GMC-SF), and interleukin-6 (IL-6) when stimulated with lipopolysaccharide in culture when compared with alveolar macrophages obtained from control subjects. Based on these observations, it was concluded that habitual exposure of the lung to marijuana impaired select functions of alveolar macrophages including their capacity to produce cytokines.

McCoy et al. (1995) assessed the ability of macrophages and macrophage-like cells exposed to THC to process and present soluble protein. THC was found to exert a differential effect on the capacity of macrophages to process antigens that are necessary for CD4+ T lymphocytes. THC inhibited the processing of hen egg lysozyme (HEL), augmented that of cytochrome *c*, and had no apparent effect on processing of ovalbumin. It was concluded that the nature of the effect of THC on antigen processing was dependent on the intrinsic conformation of the antigen itself. Matveyeva et al. (2000) extended these studies to demonstrate that the THC induced impairment of HEL processing was due, at least in part, to a selective increase in aspartyl cathepsin D proteolytic activity. It was suggested that upregulation of cathepsin D activity resulted in "over-processing" of HEL yielding peptides below the critical size required for antigen presentation. In addition, Clements et al. (1996) demonstrated that THC also suppressed a fixation-resistant co-stimulatory signal to helper T cells by diminishing expression of macrophage heat-stable antigen.

EFFECTS OF CANNABINOIDS ON CYTOKINES

A mode of action by which cannabinoids affect immunocyte functional activities, may be their capacity to express and process effector molecules, in-

cluding chemokines and cytokines. Newton et al. (1998) demonstrated that the addition of THC to murine splenocytes stimulated with pokeweed mitogen (PWM) resulted in increased levels of the cytokines interleukin-4 (IL-4) and interleukin-10 (IL-10), which are associated with Th2 responses. In contrast, THC treatment resulted in decreased levels of interferon gamma (IFN), interleukin-15 (IL-15), and interleukin-12 (IL-12), which are associated with Th1 responses. Thus, cannabinoids induced a shift in the expression of lymphocyte cytokines associated with cell-mediated immunity (i.e., Th1) versus humoral immunity (i.e., Th2). These investigators indicated also that macrophages produced a factor that was responsible for the IL-4 increase, suggesting that macrophages play a role in the Th1 versus Th2 effects. Furthermore, peritoneal macrophages directly exposed to THC and cultured in the presence of various stimulators exhibited decreased production of IL-12, IL-15, and IL-6 while demonstrating increased production of interleukin-1 alpha (IL-1), interleukin-1 beta (IL-1), and TNF . The results suggest that THC affects macrophages in splenocyte cultures and that these cells, as well as lymphocytes, are involved in alterations in levels of cytokines.

Srivastava et al. (1998) used human T, B, eosinophilic, and CD8+ NK cell lines as *in vitro* models to examine the effects of exposure to THC or the relatively non-psychotropic cannabinoid cannabidiol (CBD) on the production of cytokines and of constitutively-expressed, as well as inducibly-expressed chemokines. It was found that cannabinoids exerted a multiplicity of alterations in levels of cytokines from various immune cells. These effects were neither uniform in action nor consistent across cell lineages. THC decreased the constitutive production of the CXC chemokine interleukin-8 (IL-8), of the CC chemokines macrophage inflammatory protein-1 alpha (MIP-1), inflammatory protein-1 beta (MIP-1), and Regulated on Activation Normal T Cell Expressed and Secreted (RANTES) protein, and of phorbol ester-stimulated production of TNF , GM-CSF, and IFN by NK cells. THC also inhibited the expression of MIP-1 in human T-lymphotropic virus 1 (HTLV-1)-positive B lymphocytes. In contrast, THC treatment resulted in augmented levels of IL-8, MIP-1 , and MIP-1 in B lymphocytes and IL-8 and MIP-1 in eosinophils. Both CBD and THC inhibited the production of IL-10 in HUT-78 T cells.

Klein et al. (1993) were among the first to relate cannabinoid effects on levels of cytokines to a specific disease process. They reported that THC induces cytokine-mediated mortality of mice infected with *Legionella*. Mice receiving THC, before and after a sublethal injection of *Legionella*, experienced acute collapse and death. The THC-induced mortality resembled cytokine-mediated shock. Acute phase sera from THC-treated animals contained significantly elevated levels of TNF and IL-6 implicating these cytokines as causative, at least in part, of the enhanced mortalities. Mice receiving a normally sub-lethal in-

jection of *Legionella* and administered anti-TNF , anti-IL-6, or a mixture of anti-IL-1 and anti-IL-1 antibodies before the second THC injection, were protected from THC-induced mortalities. Antibodies against IL-6 were shown to be the most effective in rendering protection. Subsequent experiments performed on cultured splenocytes obtained from mice infected with *Legionella* and administered THC demonstrated alterations in levels of cytokines that were attributable to T lymphocyte subsets (Newton et al. 1994). Splenocytes from THC-treated infected animals stimulated in culture with mitogen were deficient in IFN production. In addition, increased production of antibody to *Legionella* of the IgG_1 isotype, as compared to that for the IgG_{2a} isotype, was observed in sera of infected mice treated with THC. Furthermore, THC treatment of cultured, normal splenocytes stimulated with mitogen resulted in production of relatively higher levels of IL-4 as compared with those for IFN . In additional studies, Klein et al. (2000) reported that THC treatment of mice suppressed early IFN , IL-12, and IL-12 receptor beta 2 responses to *Legionella pneumophila* infection. The Th2-promoting cytokine, IL-4, was increased upon infection with *Legionella* and this increase was augmented following THC administration. However, it was suggested that suppression of Th1 immunity to *Legionella* was not due to an increase in production of IL-4 but rather to a decrease in that of IFN and IL-12. Collectively, the studies performed using *Legionella* as an infectivity model suggest that cannabinoids cause a disruption of the network of cytokines which results in a shift from Th1 to Th2 lymphocyte subtype activity. This cannabinoid-mediated shift in Th1 versus Th2 cytokine activity could explain exacerbated infection with *Legionella*.

Massi et al. (1998) also noted that THC could cause alterations in the expression profile of cytokines. These investigators examined the effect of acute versus chronic subcutaneous administration of THC on immune functional and biochemical parameters in male Swiss mice. It was reported that acute exposure to THC had no effect on the splenocyte proliferative response to concanavalin A or on NK cell activity. However, a significant decrease in interleukin-2 (IL-2) production was noted. Chronic administration, for which mice were shown to be tolerant to THC-induced analgesia, resulted in inhibition of the splenocyte proliferative response, diminished NO activity, and reduction in levels of IL-2 and IFN .

Recent studies suggest that, in addition to cannabinoids, various endogenous fatty acid ethanolamides participate in the regulation of cytokine responses. Berdyshev et al. (1997) compared the effect of anandamide (arachidonic acid ethanolamide), palmitoylethanolamide, and THC on the production of TNF , IL-4, IL-6, IL-8, IL-10, and IFN by stimulated human peripheral blood mononuclear cells. Anandamide diminished the production of IL-6 and IL-8 at nanomolar concentrations but inhibited that of TNF , IFN , and IL-4 at

micromolar concentrations. Palmitoylethanolamide inhibited production of IL-4, IL-6, and IL-8 at concentrations similar to those of anandamide but had no effect on TNF and IFN . THC exerted a biphasic effect on the production of cytokines. Maximal inhibition of TNF , IL-6, and IL-8 occurred at nanomolar levels. However, at micromolar concentrations, THC caused an augmentation of levels of TNF , IL-6, and IL-8 as well as IFN . Molina-Holgado et al. (1997) demonstrated that the endogenous cannabinoid anandamide suppressed NO and TNF production by primary cultures of neonatal BALB/c mouse cortical astrocytes in response to exposure to Theiler's virus (TMEV) or bacterial lipopolysaccharide (LPS). These investigators suggested that anandamide might play an immunoregulatory role in the central nervous system (CNS).

Collectively, studies indicate that exogenous as well as endogenous cannabinoids affect the response profile for cytokines and that the nature of alterations is dependent on the concentration of cannabinoid applied. Immunomodulatory effects of cannabinoids on the production of cytokines may vary also as a function of age. Ramarathinam et al. (1997) reported that THC exerted a differential modulation of cytokines by lymphoid cells from young versus old mice. IL-4 and IL-10 production by lymphoid cells of older mice treated with THC was consistently up-regulated in response to stimulation with concanavalin A or anti-CD3 antibody. These observations suggest that aging may be an important variable for consideration when assessing immunomodulatory effects of cannabinoids.

The data indicating that cannabinoids can alter the expression profile of cytokines also suggest a potential for these compounds as selective modulators of pathological inflammatory processes. That is, since cannabinoids have the capacity to diminish the production of cytokines, appropriately designed analogs devoid of psychotropic properties could serve as therapeutic agents applicable of the treatment of disease marked by chronic or exacerbated production of cytokines. In this context, Shohami et al. (1997) reported that HU-211 exhibited pharmacological properties of an N-methyl-D-aspartate (NMDA)-receptor antagonist and acted as an effective cerebroprotectant in an experimental model of traumatic brain injury. The experimental model for closed head injury (CHI) exhibited edema, blood-brain-barrier disruption, motor and memory dysfunction as well as spatial and temporal induction of markers for the cytokines IL-1, IL-6, and TNF . HU-211 exerted an inhibitory effect on TNF production by affecting its post-translational maturation. It was suggested that, since cytokines may play a role in the pathophysiology of brain injury, TNF-modulating agents such as HU-211 could serve to improve final neurological outcome if administered within an early time frame following CHI. Gallily et al. (1997) extended these studies to demonstrate that HU-211 also has the ability to rescue rodents from endotoxic shock after LPS injection. HU-211 administered to BALB/c mice prior to introduction of LPS

resulted in a significant reduction in lethality. Furthermore, administration of HU-211 to Sprague-Dawley rats prior to treatment with LPS abolished the typical hypotensive response resulting from administration of endotoxin. In addition, HU-211 had a marked inhibitory effect on the ability of murine peritoneal macrophages and rat alveolar macrophages maintained in culture to produce TNF and NO in response to LPS. These data suggest that HU-211 may have therapeutic potential in the treatment of TNF -mediated pathologies. Achiron et al. (2000) indicated that HU-211 also reduces the inflammatory response in the brain and spinal cord in rats used as experimental models of autoimmune encephalomyelitis. It was suggested from these studies that HU-211 might be useful as an alternative mode of treatment of acute relapses of multiple sclerosis. In addition to the synthetic compound HU-211, the nonpsychoactive cannabis constituent cannabidiol (CBD) has been reported to act as an oral anti-arthritic therapeutic in a murine model of collagen-induced arthritis (CIA) (Malfait et al. 2000). CBD administered after the onset of clinical symptoms effectively blocked progression of arthritis and was equally effective when administered intraperitoneally or orally. Furthermore, clinical improvement was accompanied by protection of the joints against severe damage. It was postulated that CBD through its combined immunosuppressive and anti-inflammatory actions has a potent anti-arthritic effect on CIA.

MECHANISMS BY WHICH MARIJUANA AND CANNABINOIDS ALTER IMMUNE FUNCTION

Cannabis and cannabinoids exert a wide range of *in vivo* and *in vitro* effects on immune cells. Cannabinoids exert augmenting (McCoy et al. 1995; Derocq et al. 1995; Srivastava et al. 1998) as well as inhibitory effects of immune cell functions (reviewed in: Munson et al. 1976; Cabral and Dove Pettit 1998). Pross et al. (1992) reported that THC exerts concentration-dependent biphasic effects on immune cells. These investigators assessed the effect of THC on T lymphocyte stimulation with anti-CD3 antibody and revealed that lower drug concentrations increased proliferation while higher concentrations inhibited the response. Concentration-dependent augmenting effects of cannabinoids have also been observed by Derocq et al. (1995). It was reported that human tonsillar B-cells exposed to nanomolar concentrations of cannabinoid exhibited enhanced growth and that this enhancement was inhibited by pertussis toxin suggesting that a G protein-coupled receptor process was involved. The observation that SR141716A, an antagonist specific for the CB_1 cannabinoid receptor (Rinaldi-Carmona et al. 1994), had no effect on the cannabinoid-mediated increased proliferative response along with the identification of large amounts of CB_2 receptor mRNA in human B cells, suggested that the growth

enhancing activity was mediated through the CB_2 cannabinoid receptor. Biphasic effects of cannabinoids with respect to immune cell lineages have been observed by Klein et al. (1985). These investigators demonstrated that THC concentrations in the micromolar range suppressed mouse splenocyte proliferation to T cell mitogens and to the B cell mitogen LPS. However, B cells appeared to be more sensitive than T cells to the effects of THC.

Cannabinoids may alter immune cell activities by multiple modes of action. At high concentrations (i.e., 10^{-5} M or greater), THC and other cannabinoids can cause membrane perturbation and disruption. Relatively high concentrations which would account for such effects are achievable in humans in the context of immune cells which populate and circulate through the lung, an organ which would be exposed directly to marijuana smoke and hence to relatively high concentrations of exogenous cannabinoids. Physical disruption of cellular membranes could affect protein translational and post-translational events of immune cell effector molecules. Furthermore, since cannabinoids such as THC are highly lipophilic, their interaction with cellular membranes could alter membrane fluidity with consequent alterations in selective permeability (Wing et al. 1985). Such alterations in membranes may account for the reported inhibition of protein synthesis (Cabral and Mishkin 1989; Cabral and Fischer-Stenger 1994) and of molecular precursor transport by THC (Desoize et al. 1979). At lower concentrations, and at sites distal to the lung, cannabinoids may affect immune cell functions by signaling through cannabinoid receptors. Such receptors have been identified both within the brain and on cells of the immune system. The CB_1 was the first cannabinoid receptor to be identified and has been localized to neuronal tissues (Matsuda et al.1990) and testis (Galiègue et al. 1995), and to a lesser extent to immune cells (Galiègue et al. 1995; Waksman et al. 1999). The second cannabinoid receptor, the CB_2, has been observed in cells of the immune system (Munro et al. 1993; Bouaboula et al. 1993; Galiègue et al. 1995; Facci et al. 1995). Both receptors are coupled to a pertussis toxin-sensitive G_i/G_o protein (Howlett and Fleming 1984; Howlett 1985; Howlett et al. 1986; Matsuda et al. 1990). Binding of cannabinoid ligand to cannabinoid receptors results in an increase in the affinity of GTP for the G subunit of the G protein, a decrease in affinity for GDP, and dissociation of the subunit from the G protein complex. The dissociated G subunit interacts with adenylate cyclase to inhibit its activity resulting in decreases in levels of the second messenger cAMP (Howlett 1984; Howlett et al. 1990; Felder et al. 1992; Felder et al. 1995) and initiation of mitogen-activated protein kinase (MAPK) and immediate early gene signaling pathways (Bouaboula et al. 1993, 1995, 1996). In turn, the complex of the G protein can interact with phospholipase C leading to release of inositol-tris-phosphate (IP_3), activation of IP_3-gated calcium channels, and release of Ca^{++} from intracellular stores (Netzeband et al. 1999). The complex also can activate protein kinase B

through class-1_B phosphoinositide 3′ kinases (Gomez Del Pulgar et al. 2000). A similar series of events occurs for the CB_2 cannabinoid receptor except that, in contrast to the CB_1, no modulation of N-type calcium channels (Mackie and Hille 1992) has been observed (Felder et al. 1995). Thus, interaction of cannabinoid ligands with cannabinoid receptors can activate different signal transduction pathways that could affect a diverse array of cellular functions.

The presence of CB_2 receptors within immune cells suggests a role for these receptors in their functional activities. Transcripts (i.e., mRNAs) for the CB_2 have been found in spleen and tonsils (Galiègue et al. 1995; Munro et al. 1993) and other immune tissues and cells (Munro et al. 1993; Bouaboula et al. 1993). However, in all studies reported to date, levels of message for the CB_2 have been found to exceed those for the CB_1. The distribution pattern of levels of CB_2 mRNA displays major variation in human blood cell populations with a rank order of B lymphocytes > NK cells > monocytes > polymorphonuclear neutrophils > T8 lymphocytes > T4 lymphocytes (Galiègue et al. 1995). A rank order for levels of CB_2 transcripts similar to that for primary human cell types has been recorded for human cell lines belonging to the myeloid, monocytic, and lymphoid lineages (Galiègue et al. 1995). In addition, the presence of cognate protein has been demonstrated in rat lymph nodes, Peyer's patches, and spleen (Lynn and Herkenham 1994). The differential levels of cannabinoid receptors reported for different immune cell types may account, at least in part, for the distinctive levels of sensitivity to cannabinoid mediated action on the part of immunocytes of different lineages.

Initial studies to examine the role of cannabinoid receptors in cannabinoid-mediated alteration of immune cell activities were primarily of an implicative nature. Kaminski et al. (1992, 1994) noted that suppression of the humoral immune response by cannabinoids was mediated partially by inhibition of adenylate cyclase through a pertussis toxin sensitive guanine nucleotide binding protein (G protein) coupled mechanism, implicating a cannabinoid receptor in this process. THC and the synthetic bicyclic cannabinoid CP55940 inhibited the lymphocyte proliferative response and the sheep erythrocyte IgM antibody-forming cell response of murine splenocytes to phorbol-12-myristate-13-acetate (PMA) plus the calcium ionophore ionomycin. Jeon et al. (1996) suggested that LPS-inducible NO release by the murine macrophage-like cell line RAW264.7 was suppressed by THC and other agonists by mechanisms that involved cannabinoid receptors. Furthermore, attenuation of inducible NO gene expression by THC was reported to be mediated through the inhibition of nuclear factor- B/Rel activation. In addition, Burstein et al. (1994) presented data indicating that THC-induced arachidonic acid release from mouse peritoneal cells occurred through a series of events consistent with a receptor-mediated process that involved the stimulation of one or more phospholipases.

Recent studies have focused on the definition of the cannabinoid receptor subtype, which may be linked functionally to cannabinoid-mediated alterations in immune cell functions. Waksman et al. (1999) reported that cannabinoids affected the production of inducible NO by neonatal rat microglial cells and that this effect was linked to the CB_1 receptor. The inhibitory effect was stereoselective, consistent with the involvement of a cannabinoid receptor. The dose-dependent inhibition of NO release was exerted by the receptor high affinity binding enantiomer CP55940 while a lower effect for each comparable concentration tested was exerted by the low affinity binding paired enantiomer CP56667. Furthermore, reversal in CP55940-mediated inhibition of NO release was effected when microglial cells were pretreated with the CB_1 receptor-selective antagonist SR141716A consistent with a functional linkage to the CB_1 receptor. Stefano et al. (1996) reported that the CB_1 receptor was linked also to cannabinoid-mediated alterations in the production of constitutive NO. However, in contrast to effects on inducible NO, cannabinoid receptor agonists increased constitutive NO levels in cultures of human monocytes. As in the case of effects on inducible NO, the effect on constitutive NO production was reversed by the CB_1 receptor antagonist SR141716A supporting that the CB_1 receptor was involved in the augmentation process.

Smith et al. (2000) indicated that the CB_1 receptor played a role in the modulation of cytokine production in response to cannabinoid ligands. Two cannabinoid receptor agonists, WIN 55212-2 and HU-210, were examined for their effects on LPS-induced cytokine production in *Corynebacterium parvum* (*C. parvum*)-primed and unprimed mice. Both cannabinoids, when administered to mice before LPS, decreased serum levels of TNF and IL-12 while increasing those for IL-10. The two agonists also protected *C. parvum*-primed mice against the lethal effects of LPS. These cannabinoid-induced effects on cytokine production were reversed by the CB_1 receptor antagonist SR141716A, but not by the CB_2 receptor-specific antagonist SR144528, consistent with a functional linkage to the CB_1 receptor. Moreover, it was reported that SR141716A when administered alone modulated cytokine responses in a fashion comparable to that of WIN55212-2 and HU-210 suggesting that it could act as a partial agonist of the CB_1 receptor.

There is a larger body of data which supports the CB_2 cannabinoid receptor as linked functionally to cannabinoid-mediated alteration of immune functions. McCoy et al. (1999) implied that a functional linkage existed between cannabinoid-mediated inhibition of antigen processing by macrophages and the CB_2 receptor. In their studies, processing of HEL was inhibited by THC and other cannabinoid agonists. Stereoselective cannabinoid enantiomers showed a differential inhibitory effect for the bioactive enantiomer CP55940 versus that of its less bioactive paired enantiomer CP56667. Furthermore, the CB_1-selective antagonist SR141716A did not block the inhibitory effect of the

cannabinoid agonist while the CB_2-selective antagonist SR144528 (Rinaldi-Carmona et al. 1998) did. Zhu et al. (2000) reported that THC inhibits antitumor immunity by a CB_2 receptor-mediated, cytokine-dependent pathway. Accelerated growth of tumor implants was observed following intermittent administration of THC in two weakly immunogenic lung cancer mouse models. In contrast to the results obtained with immunocompetent mice, THC had no effect on tumor growth of implants in severe combined immunodeficiency (SCID) mice. It was demonstrated, in addition, that levels of the immune inhibitory cytokines IL-10 and transforming growth factor beta (TGF) were increased at the tumor site as well as in the spleens of mice administered THC. This augmentation was accompanied by a decrease in levels of IFN at both sites. The THC-augmentation of tumor growth was prevented by administration of anti-IL-10 or anti-TGF neutralizing antibodies. The investigators demonstrated further that administration of the CB_2 cannabinoid receptor antagonist SR144528 blocked the effects of THC. The collective results indicated that THC inhibited antitumor activity and that it did so through a CB_2 cannabinoid receptor-mediated, cytokine-dependent mode.

Derocq et al. (2000) suggested a role for the CB_2 cannabinoid receptor in cell differentiation. These investigators applied Affymetrix DNA chips to the investigation of the gene expression profile of human promyelocytic HL-60 cells transfected with the CB_2 receptor and activated with the synthetic cannabinoid agonist CP55940. Treatment of these cells with CP55940 resulted in activation of a mitogen-activated protein kinase cascade and a receptor desensitization consistent with a functional coupling of the transfected receptors. Activation of the CB_2 receptors at the genomic level effected an up-regulation of genes involved in cytokine synthesis, regulation of transcription, and cell differentiation. A majority of the genes affected were recognized as under the control of nuclear factor-kappa B (Nf B). Many features of the transcriptional events observed by Derocq et al. (2000) appeared to be related to activation of cell differentiation suggesting that the CB_2 receptor plays a role in the initialization of cell maturation. Buckley et al. (2000), employing CB_2 cannabinoid receptor knockout mice to assess the effect of THC on T cell co-stimulation, confirmed the role of the CB_2 cannabinoid receptor as linked functionally to immunomodulation. THC was shown to inhibit helper T cell activation through macrophages derived from wild-type, but not from knockout mice, indicative of at least this immune effect as mediated by the CB_2 receptor. In contrast, central nervous effects of cannabinoids remain unaffected in the knockout mice.

There have been few studies that have addressed the role of cannabinoid receptors in cannabinoid-mediated alterations in resistance to infectious agents. Noe et al. (1998), using syncytial formation as a barometer of infection, reported that cannabinoid receptor agonists enhanced syncytia formation in MT-2 cells infected with cell free human immunodeficiency virus MN strain

(HIV-1MN). Gross et al. (2000) implicated the CB_1 receptor as linked functionally to cannabinoid effects on *Brucella suis* growth within macrophages. The CB_1-selective antagonist SR141716A effected a dose-dependent inhibition of the intracellular multiplication of this gram-negative bacterium. The nonselective cannabinoid receptor agonists CP55940 or WIN55212-2 reversed the SR141716A-mediated effect. These results suggested that the CB_1 antagonist could be beneficial as an inhibitor of macrophage infection by the intracellular pathogen *Brucella suis*.

Because individual immune cells may express both CB_1 and CB_2 receptors, a complex network of cellular signal transductional pathways may be activated upon exposure to cannabinoids. Thus signaling through cannabinoid receptors may lead to additive effects as well as to immune cell functional events characterized by augmentation as well as inhibition within the same cell. Indeed, Massi et al. (2000) reported that both types of cannabinoid receptors are involved in mediating NK cell cytolytic activity. Inhibition of NK cell activity by THC was partially reversed by both the CB_1 and the CB_2 antagonists, although the CB_1 antagonist was more effective. These investigators demonstrated, also, that both antagonists reversed completely THC-mediated inhibition of IFN production. A similar outcome was obtained by Klein et al. (2000), who indicated that THC treatment suppressed immunity and early IFN, IL-12, and IL-12 receptor 2 responses to *Legionella pneumophila* infection. Furthermore, these investigators demonstrated that the suppressive effects were attenuated by CB_1 and the CB_2 antagonists, suggesting that suppression of the Th1-promoting cytokines was linked to both cannabinoid receptors. McCoy et al. (1995) reported that distinctive receptor-mediated functional outcomes may be operative within the same immune cell type. These investigators observed that comparable concentrations of THC induced enhancement of macrophage processing of cytochrome *c* while simultaneously inhibiting that of hen egg lysozyme (HEL). Furthermore, cannabinoids may exert their effects by both receptor- and non-receptor-mediated modes within the same cell type. Felder et al. (1992) demonstrated that cannabinoid agonists stimulated receptor- and non-receptor-mediated signal transduction pathways. Fibroblast cell lines which had been transfected with a recombinant cannabinoid receptor expression vector and which expressed cannabinoid receptors were used in their studies. Experiments using the synthetic cannabinoid receptor agonist CP55940 indicated that the cloned receptors coupled to the inhibition of cAMP accumulation as anticipated for the involvement of a cannabinoid receptor-linked event. However, CP55940 also stimulated the increase of free arachidonic acid in a non-stereoselective fashion indicative of the absence of a functional linkage to a cannabinoid receptor for this cellular activity.

Whether cannabinoids interact with target immunocytes by a receptor- or non-receptor mediated mode, the fundamental result is that basic functional

activities of cells are altered which often are mediated through second messenger systems. Herring and Kaminski (1999) indicated that cannabinol (CBN) mediated inhibition of NF B, cAMP response element (CRE)-binding protein, and IL-2 secretion by phorbol ester plus calcium ionophore (PMA/Io) stimulated thymocytes. CBN decreased CRE and NF B binding activity that had been induced by PMA/Io. Both a major CRE DNA binding complex comprised of a cAMP response element-binding protein (CREB)-1 homodimer, as well as a minor CREB-1/activating transcription factor (ATF)-2 complex, were inhibited. In addition, CBN diminished the binding activity of PMA/Io-inducible and non-inducible B DNA binding complexes. In PMA/Io-stimulated thymocytes, CBN effected a decrease in phosphorylation of CREB/ATF nuclear proteins, and prevented phosphorylation-dependent degradation of the NF B inhibitory protein I B . Herring and Kaminski (1999) suggested that these results indicated a functional link between CBN-mediated inhibition of thymocyte functional activities, including IL-2 production, and inhibition of the transcriptional factor activities of complexes in the CREB/ATF and NF B/Rel families. These studies were extended by Yea et al. (2000) to demonstrate that inhibition of IL-2 production by CBN was mediated through the inhibition of IL-2 gene transcription. Electrophoretic mobility shift assays demonstrated that CBN inhibited the DNA binding activity of nuclear factor of activated-T cells (NF-AT) and activator protein-1 (AP-1) in a time- and concentration-dependent manner in activated EL4 T-cells. Furthermore, the AP-1 activity was reported to be negatively regulated through inhibition of its protein components, *c-fos* and *c-jun* (Faubert and Kaminski 2000). Thus, the CBN inhibited binding to AP-1 containing sites from the IL-2 promoter was due, in part, to decreased nuclear expression of *c-fos* and *c-jun*. In addition, it was reported that the effects of CBN were due to post-translational modification of these phosphoproteins and that CBN inhibited the activation of ERK MAP kinases. Based on these studies, it was concluded that CBN-induced immunosuppression involved a disruption of the ERK signaling cascade. However, whether a cannabinoid receptor is involved in this transductional cascade of events remains unresolved.

CANNABINOIDS, CANNABIS, AND AIDS

Many studies using *in vitro* and *in vivo* models have addressed the effects of cannabinoids and cannabis on host resistance and immunity. However, there have been few studies that have assessed directly the effects of marijuana usage or of cannabinoid administration in humans. The scarcity of data applies particularly to the evaluation of effects of marijuana, used either in a recreational or therapeutic mode, among humans who have immune deficiencies.

Epidemiological studies similar to those that have been performed to assess effects of tobacco have not been carried out in human populations in relation to infection with the human immunodeficiency virus (HIV). The studies performed to date have yielded limited and often contradictory results as to effects of cannabinoids on human immunity and resistance to infection.

Wallace et al. (1998) examined risk factors and outcomes associated with identification of *Aspergillus* in respiratory specimens from individuals with HIV disease as part of a study to evaluate pulmonary complications of HIV infection. It was indicated that a substantially greater proportion of patients with *Aspergillus* as compared with control subjects died during the study. However, the use of cigarettes and marijuana was found not to be associated with *Aspergillus* respiratory infection. In contrast, Johnson et al. (1999) suggested that marijuana smoking could increase the risk of development of sino-orbital aspergillosis in patients with acquired immune deficiency syndrome (AIDS). DiFranco et al. (1996), through the San Francisco Men's Health Study (SFMHS), evaluated the association of specific recreational drugs and alcohol with laboratory predictors of AIDS. Participants in the study were evaluated at entry into the program in 1984 and in the context of the development of AIDS during six years of follow-up. No substantial association could be obtained between the use of marijuana and the development of AIDS among HIV-infected men. Similarly, Timpone et al. (1997) reported that cannabinoid use in a therapeutic mode exerted few deleterious effects, at least as they related to immune competence and resistance to infection. Persaud et al. (1999) conducted a cross-sectional survey among 124 street- and brothel-based female commercial sex workers in Guyana. No statistically significant association was found between HIV infection and marijuana use.

On the other hand, other studies have suggested that cannabinoids or marijuana exert deleterious effects as they relate to HIV infection. Stefano et al. (1998) reported that long-term exposure of human saphenous vein or thoracic artery endothelium to the human immunodeficiency virus (HIV) envelope protein gp120 in concert with morphine and/or anandamide increased endothelial adhesion of monocytes. It was suggested that enhancement of monocyte adherence was a result of desensitization of the endothelium to further NO release after initial exposure to either anandamide or morphine. The investigators suggested that abuse of opiates and/or cannabinoids could result in higher viral load in the central nervous system. Furthermore, they suggested that the increase in monocyte adherence and mobility indicative of a higher level of transmembrane migration could contribute to a more rapid progression of the AIDS. Tindall et al. (1988) conducted immunoepidemiological studies using univariant and multivariant analyses and implied an association between marijuana use and progression of HIV infection. Caiaffa et al. (1994) indicated that smoking illicit drugs such as marijuana, cocaine, or crack, *Pneumocystis ca-*

rinii pneumonia, and immunosuppression increased risk of bacterial pneumonia in HIV-seropositive users. More recently, Whitfield et al. (1997) examined the impact of ethanol and Marinol /marijuana usage on HIV+/AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, or dideoxyinosine therapy. In HIV+/AIDS patients with the lowest CD4+ counts (those not on DDI monotherapy), utilization of Marinol /marijuana did not seem to have a deleterious effect. However, Marinol /marijuana usage was associated with depressed CD4+ counts and elevated amylase levels within the DDI subgroup. Furthermore, Marinol /marijuana use was associated with declining health status in both the AZT and AZT/DDC groups.

CONCLUSION

The cumulative data obtained through cell culture studies using various immune cell populations extracted from animals or humans, together with those obtained using animal models of infection, are consistent with the proposition that marijuana and cannabinoids alter immune cell function and can exert deleterious effects on resistance to infection in humans. Both receptor- and non-receptor mediated modes of action have been proposed to account for the effects of cannabinoids. However, few controlled longitudinal epidemiological and immunological studies have been undertaken to correlate the immunosuppressive effects of marijuana smoke or cannabinoids on the incidence of infections or viral disease in humans. Clearly, additional investigation to resolve the long-term immunological consequences of cannabinoid and marijuana use as they relate to resistance to infections in humans is warranted. There is also emerging evidence that select cannabinoid compounds, particularly those devoid of psychotropic properties, may be useful for therapeutic application for pathologies characterized by chronic activation of immune cells or imbalance in expression of Th1 versus Th2 cytokines.

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Effects of Smoked Marijuana on the Lung and Its Immune Defenses: Implications for Medicinal Use in HIV-Infected Patients

Donald P. Tashkin

SUMMARY. Habitual marijuana smoking may cause a number of potentially harmful effects on the lung, including the following: (1) acute and chronic bronchitis; (2) extensive histopathologic alterations in the cells lining the bronchial passages that could impair mucociliary clearance or predispose to malignancy; (3) increased accumulation of inflammatory cells (alveolar macrophages) in the lung; and (4) impairment in the function of these important immune-effector cells, including their ability to kill microorganisms and to produce protective pro-inflammatory cytokines. The major potential pulmonary consequences of habitual marijuana use are pulmonary infection and respiratory cancer. Infectious complications could be due to smoking-related damage to the mucociliary clearance mechanism, marijuana-related impairment in the antimicrobial function of alveolar macrophages and/or fungal or bacterial contamination of marijuana. Patients with pre-existing immune deficits

Donald P. Tashkin, MD, is affiliated with the Division of Pulmonary and Critical Care Medicine, UCLA School of Medicine.

Address correspondence to: Donald P. Tashkin, MD, Professor of Medicine, Department of Medicine, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095-1690 (E-mail: dtashkin@mednet.ucla.edu).

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due to AIDS could be particularly susceptible to pulmonary infectious complications of marijuana use. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>*

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INTRODUCTION

In view of the continuing interest in the medical application of marijuana for treatment of AIDS-related symptoms, it is important to re-examine the effects of marijuana smoking on the lung and its biologic defenses against infection. This issue is of practical importance in assessing the risk-benefit ratio of cannabis therapy in the immune-suppressed patient, i.e., the relative risk of pneumonia and other potential, serious infectious complications of marijuana in relation to its possible benefits in stimulating appetite, combating nausea, relieving pain, etc. The present review will focus mainly on human observational and epidemiological studies conducted within the past two decades pertaining to the impact of marijuana smoking on lung structure and function and on respiratory illness. The reader is referred to a recent review article that also addresses the airway effects of illicit smoked substances (Tashkin 2001).

EFFECTS ON RESPIRATORY SYMPTOMS

Three separate community-based studies reported within the past 15 years have shown that habitual daily or near-daily use of marijuana is associated with both chronic and acute respiratory symptoms, indicative of chronic and acute bronchitis.

In a Los Angeles-based convenience sample of 144 daily smokers of marijuana only (MS, mean age 32 yrs), 135 smokers of both marijuana and tobacco (MTS, mean age 34 yrs), 70 smokers of tobacco only (TS, mean age 37 yrs) and 97 nonsmokers (NS, mean age 32 yrs), MS had a significantly higher prevalence than NS ($P < 0.05$) of chronic cough (18% vs. 0%, respectively), chronic sputum production (20% vs. 0%), wheeze (25% vs. 3.5%) and episodes of acute bronchitis (13% vs. 2%) (Tashkin et al. 1987). Chronic cough was defined as cough on most days for at least three months a year for two or more consecutive years and conforms to the accepted definition of "chronic bronchitis" (American Thoracic Society 1987). In contrast, the prevalence of

symptoms of chronic and acute bronchitis did not differ significantly between MS and TS, and no additive effects of marijuana and tobacco were found.

In a parallel Tucson-based study of young (mean 27 yrs) MS (n = 54), MTS (n = 56), TS (n = 20) and NS (n = 502) recruited from a random stratified cluster of households in the community, significantly more MS than NS reported cough, sputum, wheeze and shortness of breath ($p \leq 0.05$) (Bloom et al. 1987). Moreover, an additive effect of marijuana and tobacco on chronic respiratory symptoms was noted, in contrast to the findings from the Los Angeles study (Tashkin et al. 1987).

In a more recent study of 91 cannabis-dependent subjects selected from a total of 943 young adults 21 yrs of age who comprised a birth cohort born in Dunedin, New Zealand, respiratory symptoms were significantly more frequent in cannabis-dependent, nonsmokers of tobacco compared to non-tobacco smoking controls, including early morning sputum production (144% higher prevalence); wheezing apart from colds (61%); exertional dyspnea (65%); and night-time awakenings with chest tightness (72%) (Taylor et al. 2000). Interestingly, the prevalence of respiratory symptoms in cannabis-dependent subjects was similar to that in smokers of ≤ 1/2 pack of tobacco cigarettes/day.

EFFECTS ON LUNG FUNCTION

Findings from the three community-based studies of the pulmonary status of regular marijuana users cited above have revealed conflicting effects of habitual marijuana use on lung function. In the Tucson study, MS, compared to NS, showed significantly lower values for the ratio of forced expired volume in one second (FEV_1) to forced vital capacity (FVC), a sensitive and specific indicator of airflow obstruction (Bloom et al. 1987). Even lower values for FEV_1/FVC ratio were observed in MS than TS, although the mean values for this measure were still within statistically normal limits. From these observations the authors concluded that regular marijuana smoking among young individuals may be an important risk factor for the subsequent development of obstructive airways disease. A follow-up study of the same cohort demonstrated a significant reduction in FEV_1 and FEV_1/FVC ratio in relation to previous use of marijuana, a finding that was interpreted as suggesting that continuing marijuana smoking may lead to a progressive decline in lung function (Sherrill et al. 1991).

In the more recent study from New Zealand, 36% of 21-yr-old cannabis-dependent subjects (two-thirds of whom had developed cannabis dependence since age 18), demonstrated a reduced FEV_1/FVC ratio (< 0.80), compared to only 20% of the nonsmokers from the same birth cohort ($p = 0.04$) (Taylor et al. 2000). The authors concluded that only a relatively short duration of heavy

cannabis use can lead to early airways obstruction in young individuals. It is not clear, however, whether adequate adjustment was made for the possible confounding of these findings by concomitant tobacco use.

The above findings are not supported by the results of the Los Angeles study of 124 MS, 56 TS, 113 MTS and 92 NS (Tashkin et al. 1987). In the latter study, no association was observed between heavy, habitual use of marijuana (mean of > 3 joints/day for > 15 yrs) and abnormalities not only in FEV_1 or FEV_1/FVC ratio, but also in even more sensitive measures of early obstructive ventilatory impairment, including forced expiratory flow rates at low lung volumes and indices derived from single-breath nitrogen washout. Abnormalities in the latter tests are commonly found in tobacco cigarette smokers, some of who are destined to develop clinically significant chronic obstructive pulmonary disease. In addition, regular use of marijuana was not associated with any abnormality in the single-breath diffusing capacity for carbon monoxide (D_LCO), a sensitive physiologic indicator of emphysema (Tashkin et al. 1987). On the other hand, regular tobacco smoking was associated with abnormalities in most of the tests of airways function, as well as in D_LCO, and heavy habitual marijuana use did not potentiate any of the adverse effects of concomitant tobacco smoking on lung function in dual smokers of marijuana and tobacco.

More recently, the Los Angeles investigators sought to determine whether regular marijuana smoking might lead to a progressive decline in lung function with age and continuing smoking that was not evident in the earlier analysis of the cross-sectional data for lung function (Tashkin et al. 1997). They measured FEV_1 sequentially at intervals of $\geq$ 1 yr for up to 8 yrs in 87 MS, 42 TS, 63 MTS and 63 NS. While they noted that tobacco smoking was associated with a significant age-related decline in FEV_1 compared to the change in NS, they were unable to detect an effect of even heavy marijuana smoking (3 joints/d) on FEV_1 decline, nor did they observe any additive effect of marijuana and tobacco. Since chronic obstructive pulmonary disease (chronic obstructive bronchitis and/or emphysema) is characterized by an excessive age-related decline in FEV_1, these findings argue against an association between regular marijuana smoking and the development of chronic obstructive pulmonary disease. This conclusion is supported by the results of earlier studies in rats exposed to progressively increasing doses of marijuana or tobacco smoke for six months in which the lungs of the tobacco-exposed rats, but *not* those of the marijuana-exposed rats or the unexposed control animals, showed anatomic and physiologic evidence of emphysema (Huber and Mahajan 1988).

EFFECTS ON AIRWAY PATHOLOGY

It is possible that habitual cannabis smoking may cause airway injury and inflammation in the absence of either respiratory symptoms or any demonstra-

ble alteration in lung function. Therefore, to determine the effects of marijuana and tobacco smoking on the gross appearance of the visible portion of the lower respiratory tract of healthy individuals, Roth et al. (1998) performed videobronchoscopy on a small cohort of 40 relatively asymptomatic nonsmokers (NS; n = 10), smokers of marijuana only (MS; n = 10), smokers of tobacco only (TS; n = 10) and smokers of both marijuana and tobacco (MTS; n = 10), all of whom had no or few abnormalities in lung function. A visual bronchitis index score was used to evaluate the presence and extent of airway erythema (redness), edema (swelling) and hypersecretion. Biopsies of the bronchial mucosa were also performed to correlate the visual endoscopic observations with microscopic histopathologic evidence of airway injury and inflammation (vascular hyperplasia, submucosal edema, inflammatory cell infiltrates and hyperplasia of surface mucus-secreting [goblet] cells). In addition, bronchial lavage (saline rinse) was performed to evaluate the peripheral airways for evidence of inflammation (reflected by increased numbers of neutrophils) and/or elevations in interleukin-8 (IL-8), a potent neutrophil chemoattractant and activator. Bronchitis index scores were found to be significantly higher in MS, TS and MTS than in NS. Bronchial mucosal biopsies were positive for two of the histopathologic features of airway injury in 97% of all smokers and for three criteria in 72%, whereas none of the biopsies from NS showed greater than one positive finding. The percentage of neutrophils in bronchial lavage fluid correlated with IL-8 levels and exceeded 20% in 0 of 10 NS, 1 of 9 MS, 2 of 9 TS, and 5 of 10 MTS. These findings suggest that regular smoking of marijuana and/or tobacco by young adults is associated with a high frequency of endoscopically and microscopically apparent airway injury and inflammation even in the absence of any symptoms or physiologic evidence of injury.

The effect of habitual use of marijuana on the microscopic pathology of the lower airways was systematically evaluated by a single "blinded" pathologist from bronchial mucosal biopsies obtained at bronchoscopy from healthy volunteer subjects participating in the Los Angeles cohort study (Fligiel et al. 1997). These subjects included 40 MS, 31 TS, 44 MTS and 53 NS, most of who did not report significant respiratory symptoms or demonstrate significant abnormalities in lung function. The histopathologic features that were examined included basal cell hyperplasia; stratification; squamous metaplasia; goblet cell hyperplasia; cellular disorganization; nuclear variation; mitotic figures; increased nuclear-to-cytoplasmic ratio; inflammation; and basement membrane thickening. Regular smoking of marijuana alone (average of 3-4 joints per day) was associated with a greater frequency and severity of abnormalities for most of the features examined compared to the changes noted in the nonsmokers and at least as extensive abnormalities as those found in the smokers of tobacco alone (22 cigarettes per day). The similar frequency and extent of bronchial histopathology in the marijuana-only compared to the tobacco-only

smokers is noteworthy in view of the marked disparity between the daily number of marijuana vs. tobacco cigarettes consumed by these two groups of subjects. Interestingly, for nearly all histological features examined, abnormalities were noted more commonly in the combined smokers of marijuana plus tobacco than in smokers of either substance alone, implying additive effects of the two smoked substances on airway injury.

These findings have the following important implications:

- Habitual marijuana smoking can cause potentially serious airway pathology at a relatively early age even in the absence of any clinical or physiologic evidence of disease.
- Regular marijuana use produces at least as much damage to the mucosa of the larger airways as the regular smoking of tobacco, despite the considerably smaller daily number of marijuana joints smoked by the MS (average of 3-4 joints/d) than the daily number of tobacco cigarettes smoked by the TS (mean of 22 cigarettes/d), suggesting that marijuana has a more damaging effect than tobacco per cigarette smoked. The similarity in airway histopathology despite the disparity in the amount of plant substance smoked might be explained, at least partly, by the four-fold increase in deposition of tar from a single marijuana cigarette compared to a tobacco cigarette of the same weight (Wu et al. 1988). The latter increase in deposition could be due to differences in cigarette filtration and smoking technique for the two types of cigarettes: marijuana cigarettes do not have filter tips, are more loosely packed and are generally smoked with a four-fold longer breathholding time than tobacco cigarettes. The differences in filtration enhance delivery of tar to the smoker's mouth from marijuana compared to tobacco cigarettes, and the far longer breathholding time employed in smoking marijuana than tobacco provides more opportunity for respiratory deposition of ultra-fine smoke particulates and absorption of toxic gas-phase constituents in the smoke (Wu et al. 1988; Tashkin et al. 1991).
- The observation that marijuana and tobacco appear to have additive effects on bronchial epithelial histopathology in the combined smokers of both substances is of concern since the prevalence of tobacco smoking is substantially higher among marijuana smokers than nonsmokers of marijuana. For example, in the UCLA cohort, approximately 50% of the marijuana smokers also smoked tobacco, whereas the prevalence of tobacco smoking among adults in California in general is approximately 20%.
- Some of the histopathologic changes in the marijuana smokers, notably the frequent loss of ciliated bronchial epithelial cells and their replacement by non-ciliated cells, such as hyperplastic mucus-secreting (goblet)

cells or reserve (basal) cells, or by metaplastic squamous epithelium, could explain the high frequency of symptoms of chronic bronchitis (chronic cough and sputum production) in smokers of marijuana alone. The hair-like projections (cilia) of the normal ciliated bronchial epithelial cells play an important role in mucociliary clearance of secretions. Excessive mucus production by hyperplastic goblet cells (and by hypertrophied submucosal mucus glands) and diminished clearance of these secretions because of the loss of cilia can lead to an accumulation of excess mucus, leaving cough as the only mechanism for mucus clearance. Since the mucus lining the airways also traps inhaled bacteria, other microorganisms and other potentially harmful particles, an intact mucociliary clearance mechanism is the lung's first line of defense against infection and other noxious insults. Marijuana-related damage to this mechanism could therefore predispose to lower respiratory tract infection and other adverse consequences of inhaled particulates.

- A carcinogenic effect of marijuana is suggested by certain histopathologic alterations in the bronchial epithelium of smokers of marijuana with or without tobacco. These include squamous metaplasia, cellular disorganization, nuclear variation, mitotic figures and increased nuclear-to-cytoplasmic ratio, which have long been considered to represent potential precursors for the subsequent development of bronchogenic carcinoma (Auerbach et al. 1961).

BRONCHIAL EXPRESSION OF IMMUNOHISTOCHEMICAL MARKERS OF DYSREGULATED GROWTH AND PRE-TUMOR PROGRESSION

A number of genetic alterations are responsible for the transformation of lung cells from normal to cancerous. Bronchial biopsies obtained in 12 MS, 14 TS, 9 MTS and 28 MTS from the UCLA cohort were therefore examined for alterations in some of the genes involved in the pathogenesis of lung cancer, as reflected by surrogate end-point markers that have been linked to an increased risk of lung cancer. Immunohistological studies of these biopsies showed marked overexpression in the bronchial epithelium of MS of Ki-67 (a marker of cell proliferation) and epidermal growth factor receptor (EGFR) (Barsky et al. 1998). Moreover, p53, one of the most common tumor suppressor genes altered in human cancers, was expressed in 11% of subjects who smoked marijuana together with tobacco. These findings suggest that smoking marijuana, like tobacco smoking, causes dysregulated growth of bronchial epithelial cells, possibly reflecting an increased risk of marijuana smokers for the subsequent development of lung cancer.

EFFECTS ON ALVEOLAR MACROPHAGES

Effects on Alveolar Macrophage Structure

Alveolar macrophages (AMs) are the major cells that reside in the peripheral air spaces of the lung and normally constitute over 90% of the cells recovered by bronchoalveolar lavage (BAL). These important immune effector cells play a crucial role in the lung's immune defense system. MS, TS and MTS all show an increase in the number of AMs recovered from the distal air spaces by BAL, compared to NS in the order of MTS > TS > MS > NS, and the effects of marijuana and tobacco smoking on the accumulation of AMs in the lung appear additive (Barbers et al. 1987). Examination of the ultrastructure of AMs recovered by BAL from smokers of marijuana and/or tobacco and nonsmokers by transmission electron microscopy has revealed marked abnormalities in the AMs of the smokers of either or both substances, consisting mainly of larger and more complex cytoplasmic inclusions than observed in the AMs of nonsmokers (Beals et al. 1989). Furthermore, ultrastructural differences were noted between the AMs of MS and TS, suggesting that exposure to marijuana or tobacco could lead to differences in the functional activity of these cells.

Effects on Alveolar Macrophage Function

The functional activity of human alveolar macrophages has been assessed by examination of their microbicidal activity and their production of reactive oxygen species, reactive nitrogen intermediates and inflammatory cytokines.

MICROBICIDAL ACTIVITY

AMs from both MS and TS have been shown to be impaired in their ability to kill *Candida albicans* (Sherman et al. 1991a) and *Candida pseudotropicalis* (Baldwin et al. 1997) compared to AMs from NS, although no defect in phagocytosis for fungi was noted (Sherman et al. 1991a). AMs from MS, but not those from TS, have also been shown to be deficient in their ability both to phagocytose and to kill the pathogenic bacterium, *Staphylococcus aureus*. The cause of these marijuana-related deficits in AM fungicidal activity and bacterial phagocytosis and killing is unclear but could be due, at least partly, to marijuana-induced deficiencies in the production of toxic oxygen species or reactive nitrogen intermediates, such as nitric oxide.

PRODUCTION OF REACTIVE OXYGEN SPECIES ("RESPIRATORY BURST")

Earlier studies demonstrated a reduced ability of AMs from MS to generate superoxide anion (O_2) both under basal conditions (compared to AMs from either NS or TS) and when stimulated (compared to AMs from TS), in contrast to an enhanced generation of O_2^- by AMs from TS under both basal and respiratory-burst stimulated conditions (Sherman et al. 1991a,b). Since reactive oxygen species serve as important effector molecules for microbial killing, the different respiratory burst characteristics of AMs from MS compared to those of AMs obtained from TS imply that different mechanisms may contribute to impairment of fungicidal activity of alveolar macrophages derived from smokers of these two different substances. It is tempting to speculate, however, that, since oxidants, including O_2^-, released from AMs, can also cause lung tissue injury, the marijuana-related impairment in the respiratory burst activity of AMs may provide protection against smoke-related damage to the peripheral airways and alveoli. Thus, it is possible that the dampening effect of marijuana smoking on the production of toxic oxygen radicals by immune effector cells in the lung could account for the absence of abnormalities in small airways function and alveolar diffusing capacity (physiologic markers of tobacco-related small airways disease and/or emphysema) in smokers of marijuana alone, in contrast to the presence of such physiologic abnormalities in smokers of tobacco, with or without marijuana (Sherman et al. 1991a,b).

PRODUCTION OF REACTIVE NITROGEN INTERMEDIATES AND PRO-INFLAMMATORY CYTOKINES

Preliminary data suggest that the impairment in the bactericidal activity of AMs from MS may be due to a marijuana-related impairment in production of reactive nitrogen intermediates (e.g., nitric oxide), which also serve as important effector molecules in bacterial killing. This impairment, in turn, could be secondary to a marijuana-related inhibition of AM production of inducible nitric oxide synthase (iNOS) in the course of infection (Baldwin et al. 2000). *In vitro* studies using AMs from MS in killing assays for *S. aureus* in the presence or absence of an inhibitor of iNOS with and without the addition of specific pro-inflammatory cytokines (interferon- [INF] and granulocyte-macrophage colony stimulating factor [GM-CSF]) suggest that the inhibition in bactericidal activity may be due to a marijuana-related impairment in production of key cytokines (e.g., INF and GM-CSF) that mediate the induction of iNOS. Other data indicating an inhibition of lipopolysaccharide-stimulated production of TNF- , IL-6 and GM-CSF by AMs from MS but not from TS provide further support for this hypothesis (Baldwin et al. 1997).

EFFECTS ON OTHER IMMUNE CELLS

Several *in vitro* and animal studies suggest that ^{9}-tetrahydrocannabinol (THC) is a powerful immune modulator and that it has a predominantly immunosuppressive effect on a variety of immune cells, including macrophages, natural killer cells and T lymphocytes (Klein, Friedman and Specter 1998). These observations are consistent with the finding of cannabinoid (CB) receptors on immune cells (Bouaboula et al. 1993). The immunosuppressive effect of THC appears to be due to its inhibition of lymphocyte production of immunostimulatory helper T cell type-1 cytokines (e.g., interleukin-2 [IL-2] and interferon gamma [IFN-]) and its parallel promotion of the production of immunoinhibitory helper T cell type-2 cytokines, such as interleukin-10 [IL-10] and interleukin-4 [IL-4] (Newton, 1994). It is possible that this immunosuppressive effect of THC could impair the host's ability to develop an anti-bacterial immune response and thereby facilitate bacterial infection. This possibility was studied in a mouse model of *Legionella pneumophila,* a cause of community-acquired and opportunistic pneumonia (Newton, Klein and Friedman 1994). Mice pre-treated with ^{9}-THC prior to infection with a sublethal dose of *L. pneumophila* failed to develop cell-mediated protective immunity and died when re-challenged with the organism, while control mice not pre-treated with ^{9}-THC became immune to repeated infection and survived. It is possible that a similar mechanism could be responsible for an increased predisposition of human users of marijuana to pulmonary infection.

CLINICAL IMPLICATIONS

The clinical implications of the above findings concerning the impact of regular marijuana smoking on the microbicidal activity of human AMs, as well as the inhibitory effect of THC on the ability of experimental animals to develop a protective anti-bacterial immune response, are that marijuana smoking may impair the lung's defense against infection, in part due to impairment in the critical antimicrobial function of alveolar macrophages, thus predisposing to pneumonia. The associated impairment in tracheobronchial mucociliary function (implied by the histopathologic evidence of marijuana-associated damage to the normal ciliated epithelial lining of the lower respiratory tract) further undermines the ability of the lung to defend itself against infections. In marijuana smokers with HIV infection, the combined effects of these two factors could add to the already increased risk of immunosuppressed patients with AIDS for pulmonary infection. The reported frequent contamination of marijuana with the fungus, *Aspergillus fumigatus*, (Kagen et al. 1983) and with potentially pathogenic gram-negative bacteria (Ungerleider et al. 1982) could

further heighten the risk of opportunistic fungal and bacterial pneumonia in the immunocompromised patient. A few clinical case reports and limited epidemiological studies (*vide infra*) provide some clues, but as yet no definitive evidence, as to the real risks of immunocompromised patients for the development or respiratory infection as a complication of marijuana smoking.

CLINICAL CASE REPORTS

Several clinical cases have been reported of invasive *Aspergillus* pneumonia in immunocompromised patients, including patients with AIDS (Denning et al. 1991), chronic granulomatous disease (Chusid et al. 1975), bone marrow transplantation (Hamadeh et al. 1988), renal transplantation (Marks et al. 1996) or small cell lung cancer treated with chemotherapy (Sutton, Lum, and Torti 1986), all of whom smoked marijuana. The precise role of marijuana in these cases of invasive pulmonary aspergillosis is unclear. While it is possible that the opportunistic fungal pulmonary infection in these patients may have been due primarily to their underlying immune compromise in the face of possible contamination of marijuana with *Aspergillus* (Kagen et al. 1983), the further possibility that an independent superimposed effect of marijuana smoking on pulmonary host defenses was a critical factor cannot be excluded. It is also possible that habitual marijuana smokers without any identifiable underlying immune deficiency could be predisposed to pulmonary infection as a consequence of the deficits in the lung's host defense caused by regular cannabis use. Recently, a 23-yr-old heavy smoker of both marijuana and tobacco with a history of intravenous opioid use but no clinical evidence of an underlying immune deficiency was reported to have developed miliary necrotizing granulomata, associated with progressive exertional dyspnea, bilateral nodular pulmonary infiltrates and a blackened alveolar exudate of carbon-laded macrophages (Cunningham et al. 2000). Although actual fungal infection was not documented, the authors suspected either infection with an unidentified fungus inhaled with the marijuana smoke or hypersensitivity to inhaled fungi as the most likely cause of the necrotizing granulomata.

EPIDEMIOLOGICAL STUDIES

Outpatient Visits for Respiratory Illness

In an epidemiological cohort study of the impact of marijuana smoking on the health care utilization of Kaiser Permanente health plan members, marijuana smoking history was ascertained from a comprehensive, multi-phasic health screening questionnaire and the medical experience of daily or near-

daily users of marijuana who never smoked tobacco (n = 452), as ascertained from medical records reviews, was compared with that of a demographically similar group of nonsmokers of either substance (n = 450) (Polen et al. 1993). Frequent marijuana smokers had small but significantly increased risks of outpatient visits for respiratory illness (relative risk [RR] = 1.19; 95% C.I. = 1.02, 1.16), as well as for other types of illness, compared with nonsmokers, in addition to a small increased risk of hospitalization. Neither independent nor additive or interactive effects of tobacco combined with marijuana were examined in this study.

Studies in Subjects with AIDS or HIV-Seropositivity

In an early, small-scale case-control study of 31 patients with severe manifestations of AIDS (13 with confirmed Kaposi's sarcoma and 18 with an opportunistic infection) compared with 29 symptom-free patients referred with possible AIDS, marijuana use was associated with a significantly increased risk for progression to Kaposi's sarcoma or opportunistic infection (OR = 3.7 [95% C.I. 1.10-12.30]; $p < 0.05$) (Newell et al. 1985). In another early prospective study in which logistic regression was used to assess lifestyle factors associated with progression or non-progression of 386 HIV seropositive individuals to end-stage AIDS within 2-3 years of enrollment, marijuana use in the preceding 3 months was identified as one of only two lifestyle factors or the only factor associated with progression to AIDS (n = 32) in univariate or multivariate analyses, respectively (Tindall et al. 1988). A more recent cohort study of risk factors for the first episode of bacterial pneumonia in 629 HIV-seropositive injection drug users (IDUs), of whom 40 subsequently developed pneumonia, revealed that smoking illicit substances (marijuana or crack cocaine) was significantly associated with the development of bacterial pneumonia in multivariate analysis (OR = 2.24; 95% C.I. 1.03-4.89) (Caiaffa et al. 1994). It is particularly noteworthy that among HIV-seropositive IDUs with a previous history of *Pneumocystis carinii* pneumonia, smoking illicit drugs had the strongest effect on risk of bacterial pneumonia (OR = 22.94; 95% C.I. 2.18-241.10). These few epidemiological studies suggest that HIV-seropositive patients who smoke marijuana regularly may be particularly vulnerable to opportunistic pulmonary infection. However, the possible incrimination of marijuana smoking for predisposing HIV-seropositive patients to pneumonia requires further investigation by more rigorous epidemiological studies, particularly in view of the growing interest in medicinal marijuana for patients with AIDS.

Mortality

The relationship of marijuana use to mortality was examined in a cohort of 65,171 Kaiser Permanente health care members, 15-49 yrs of age, who com-

pleted health-screening questionnaires that included questions on marijuana use (Sidney et al. 1997). Follow-up for assessing mortality was conducted for 6-12 yrs following questionnaire completion. Current marijuana use was not associated with a significantly higher risk of mortality in either men or women, compared with nonuse, except for an increased risk of death due to AIDS in men. However, the latter association was felt to be due to confounding by male homosexual behavior among the current marijuana smokers, rather than an effect of marijuana itself on mortality due to AIDS.

OTHER CLINICAL CONSEQUENCES

Barotrauma and Lung Bullae

Isolated cases of spontaneous pneumothorax and/or pneumomediastinum have been temporally associated with marijuana use (Feldman et al. 1993; Mattox 1976; Miller. Spiekerman and Hepper 1972). These complications are believed to involve barotrauma to the lung from the increased intrathoracic pressure that develops when a marijuana smoker performs a Valsalva maneuver against a closed glottis after deep inhalation of the smoke in an effort to “pressurize” the smoke within the lung to enhance absorption of THC. Several cases of large upper zone lung bullae have recently been reported in otherwise healthy young male marijuana smokers with relatively little exposure to tobacco (Johnson et al. 2000) The mechanism for bulla formation in these cases could be due to a direct toxic effect of components in marijuana smoke on the lungs of susceptible smokers and/or airway barotrauma related to the high intrathoracic pressures generated during marijuana smoking. The clinical significance of pneumothorax and/or pneumomediastinum could be exaggerated in patients with AIDS who already have pulmonary deficits due to effects of current or previous pulmonary infectious or noninfectious pulmonary complications of AIDS.

CONCLUSION

Frequent marijuana use can cause airway injury, lung inflammation and impaired pulmonary defense against infection. The major potential pulmonary consequence of habitual marijuana use of particular relevance to patients with AIDS is superimposed pulmonary infection, which could be life threatening in the seriously immunocompromised patient. In view of the immunosuppressive effect of THC, the possibility that regular marijuana use could enhance progression of HIV infection itself needs to be considered, although this possibility remains unexplored to date. A few mainly older epidemiological studies in

HIV-positive individuals have identified marijuana use as a significant risk factor for acquisition of opportunistic infections and/or Kaposi's sarcoma. Further investigation of the real risks of pulmonary complications from regular marijuana use by HIV-positive patients is required using rigorous epidemiological methodology.

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Cannabis and Cannabis Extracts: Greater Than the Sum of Their Parts?

John M. McPartland
Ethan B. Russo

SUMMARY. A central tenet underlying the use of botanical remedies is that herbs contain many active ingredients. Primary active ingredients may be enhanced by secondary compounds, which act in beneficial synergy. Other herbal constituents may mitigate the side effects of dominant active ingredients. We reviewed the literature concerning medical cannabis and its primary active ingredient, Δ^9-tetrahydrocannabinol (THC). Good evidence shows that secondary compounds in cannabis may enhance the beneficial effects of THC. Other cannabinoid and non-cannabinoid compounds in herbal cannabis or its extracts may reduce THC-induced anxiety, cholinergic deficits, and immunosuppression. Cannabis terpenoids and flavonoids may also increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide anti-inflammatory activity.

John M. McPartland, DO, MS, is affiliated with GW Pharmaceuticals, Ltd., Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, UK.

Ethan B. Russo, MD, is affiliated with Montana Neurobehavioral Specialists, 900 North Orange Street, Missoula, MT 59802 USA.

Address correspondence to: John M. McPartland, DO, Faculty of Health & Environmental Science, UNITEC, Private Bag 92025, Auckland, New Zealand (E-mail: jmcpartland @unitec.ac.nz).

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KEYWORDS. Cannabis, marijuana, THC, cannabinoids, phytocannabinoids, cannabidiol, cannabichromene, cannabigerol, tetrahydrocannabivarin, terpenoids, essential oils, flavonoids, herbal medicine, medicinal plants, herbal synergy

INTRODUCTION

Cannabis is an herb; it contains hundreds of pharmaceutical compounds (Turner et al. 1980). Herbalists contend that polypharmaceutical herbs provide two advantages over single-ingredient synthetic drugs: (1) *therapeutic effects* of the primary active ingredients in herbs may be *synergized* by other compounds, and (2) *side effects* of the primary active ingredients may be *mitigated* by other compounds. Thus, cannabis has been characterized as a "synergistic shotgun," in contrast to Marinol® (Δ^9-tetrahydrocannabinol, THC), a synthetic, single-ingredient "silver bullet" (McPartland and Pruitt 1999).

Mechoulam et al. (1972) suggested that other compounds present in herbal cannabis might influence THC activity. Carlini et al. (1974) determined that cannabis extracts produced effects "two or four times greater than that expected from their THC content." Similarly, Fairbairn and Pickens (1981) detected the presence of unidentified "powerful synergists" in cannabis extracts causing 330% greater activity in mice than THC alone.

Other compounds in herbal cannabis may ameliorate the side effects of THC. Whole cannabis causes fewer psychological side effects than synthetic THC, seen as symptoms of dysphoria, depersonalization, anxiety, panic reactions, and paranoia (Grinspoon and Bakalar 1997). This difference in side effect profiles may also be due, in part, to differences in administration: THC taken by mouth undergoes "first pass metabolism" in the small intestine and liver, to 11-hydroxy THC; the metabolite is more psychoactive than THC itself (Browne and Weissman 1981). Inhaled THC undergoes little first-pass metabolism, so less 11-hydroxy THC is formed. Thus, "smoking cannabis is a satisfactory expedient in combating fatigue, headache and exhaustion, whereas the oral ingestion of cannabis results chiefly in a narcotic effect which may cause serious alarm" (Walton 1938, p. 49).

Respiratory side effects from inhaling cannabis smoke may be ameliorated by both cannabinoid and non-cannabinoid components in cannabis. For instance, throat irritation may be diminished by anti-inflammatory agents, mutagens in the smoke may be mitigated by antimutagens, and bacterial contaminants in cannabis may be annulled by antibiotic compounds (McPartland and Pruitt 1997). The pharmaceutically active compounds in cannabis that enhance beneficial THC activity and reduce side effects are relatively unknown. The pur-

pose of this paper is to review the biochemistry and physiological effects of those other compounds.

MATERIALS AND METHODS

MEDLINE (1966-2000) was searched using MeSH keywords: cannabinoids, marijuana, tetrahydrocannabinol. AGRICOLA (1990-1999) was searched using the keywords cannabis, hemp, and marijuana. Phytochemical and ethnobotanical databases were searched via the Agricultural Research Service webpage <http://www.ars-grin.gov/~ngrlsb/>. All reports were scanned for supporting bibliographic citations; antecedent sources were retrieved to the fullest possible extent. Data validity was assessed by source (peer-reviewed article vs. popular press), identification methodology (analytical chemistry vs. clinical history) and the frequency of independent observations.

RESULTS AND DISCUSSION

Turner et al. (1980) listed over 420 compounds in cannabis. Sparacino et al. (1990) listed 200 additional compounds in cannabis smoke. We will highlight six cannabinoids beyond THC, a dozen-odd terpenoids, three flavonoids, and one phytosterol. Other non-cannabinoids with proven pharmacological activity include poorly characterized glycoproteins, alkaloids, and compounds that remain completely unidentified (Gill et al. 1970).

CANNABINOIDS

Mechoulam and Gaoni (1967) defined "cannabinoids" as a group of C_{21} terpenophenolic compounds uniquely produced by cannabis. The subsequent development of synthetic cannabinoids (e.g., HU-210) has blurred this definition, as has the discovery of endogenous cannabinoids (e.g., anandamide), defined as "endocannabinoids" by DiMarzo and Fontana (1995). Thus, Pate (1999) proposed the term "phytocannabinoids" to designate the C_{21} compounds produced by cannabis. Phytocannabinoids exhibit very low mammalian toxicity, and mixtures of cannabinoids are *less toxic* than pure THC (Thompson et al. 1973).

Cannabidiol (CBD) is the next-best studied phytocannabinoid after THC (Figure 1). The investigation of CBD by marijuana researchers is rather paradoxical, considering its concentrations are notably lower in drug varieties of cannabis than in fiber cultivars (Turner et al. 1980).

CBD possesses sedative properties (Carlini and Cunha, 1981), and a clinical trial showed that it reduces the anxiety and other unpleasant psychological side effects provoked by pure THC (Zuardi et al. 1982). CBD modulates the pharmacokinetics of THC by three mechanisms: (1) it has a slight affinity for cannabinoid receptors (Ki at CB1 = 4350 nM, compared to THC = 41 nM, Showalter et al. 1996), and it signals receptors as an antagonist or reverse agonist (Petitet et al. 1998), (2) CBD may modulate signal transduction by perturbing the fluidity of neuronal membranes, or by remodeling G-proteins that carry intracellular signals downstream from cannabinoid receptors, and (3) CBD is a potent inhibitor of cytochrome P450 3A11 metabolism, thus it blocks the hydroxylation of THC to its 11-hydroxy metabolite (Bornheim et al. 1995). The 11-hydroxy metabolite is four times more psychoactive than unmetabolized THC (Browne and Weissman 1981), and four times more immunosuppressive (Klein et al. 1987).

CBD provides antipsychotic benefits (Zuardi et al. 1995). It increases dopamine activity, serves as a serotonin uptake inhibitor, and enhances norepinephrine activity (Banerjee et al. 1975; Poddar and Dewey 1980). CBD protects neurons from glutamate toxicity and serves as an antioxidant, more potently than ascorbate and α-tocopherol (Hampson et al. 1998). Auspiciously, CBD does *not* decrease acetylcholine (ACh) activity in the brain (Domino 1976; Cheney et al. 1981). THC, in contrast, reduces hippocampal ACh release in rats (Carta et al. 1998), and this correlates with loss of short-term memory consolidation. In the hippocampus THC also inhibits *N*-methyl-D-aspartate (NMDA) receptor activity (Misner and Sullivan 1999; Shen and Thayer 1999), and NMDA synaptic transmission is crucial for memory consolidation (Shimizu et al. 2000). CBD, unlike THC, does not dampen the firing of hippocampal cells (Heyser et al. 1993) and does not disrupt learning (Brodkin and Moerschbaecher 1997).

Consroe (1998) presented an excellent review of CBD in neurological disorders. In some studies, it ameliorates symptoms of Huntington's disease, such as dystonia and dyskinesia. CBD mitigates other dystonic conditions, such as torticollis, in rat studies and uncontrolled human studies. CBD functions as an anticonvulsant in rats, on a par with phenytoin (Dilantin®, a standard antiepileptic drug).

CBD demonstrated a synergistic benefit in the reduction of intestinal motility in mice produced by THC (Anderson, Jackson, and Chesher 1974). This may be an important component of observed benefits of cannabis in inflammatory bowel diseases.

The CBD in cannabis smoke may explain why inhaling it causes less airway irritation and inflammation than inhalation of pure THC (Tashkin et al. 1977). CBD imparts analgesia (more potently than THC), it inhibits erythema (much more than THC), it blocks cyclooxygenase (COX) activity with a greater max-

imum inhibition than THC, and it blocks lipoxygenase (the enzyme that produces asthma-provoking leukotrienes), again more effectively than THC (Evans 1991). Mice with inflammatory collagen-induced arthritis (a mouse model for rheumatoid arthritis) were given oral CBD (5 mg/kg per day) and showed clinical improvement, and the treatment effectively blocked progression of the arthritis (Malfait et al. 2000).

CBD reportedly has little or no effect on the immune system (reviewed by Klein et al. 1998), although the mouse arthritis study by Malfait et al. (2000) showed CBD decreases the production of tumor necrosis factor (TNF) and Interferon-gamma (IFN-γ), which are two immunomodulatory cytokines described later. CBD actually kills bacteria and fungi, with greater potency than THC (Klingeren and Ham 1976; ElSohly et al. 1982; McPartland 1984). Thus, cannabis may have less microbial contamination than other herbs, an important consideration for immunocompromised individuals (McPartland and Pruitt 1997).

Cannabinol (CBN) is the degradation product of THC (Turner et al. 1980), and is found most often in aged cannabis products (Figure 1). CBN potentiates the effects of THC in man (Musty et al. 1976), yet it antagonizes the effects of THC in mice (Formukong et al. 1988). Studies reporting CBN's effects upon norepinephrine and dopamine also conflict–CBN may have negligible effects on these biogenic amines (Banerjee et al. 1975), enhance their release (Poddar and Dewey 1980), or decrease their release (Dalterio et al. 1985). CBN increases plasma concentrations of follicle-stimulating hormone, and enhances the production of testicular testosterone (Dalterio et al. 1985). CBN shares some characteristics with CBD; for example, it has anti-convulsant activity (Turner et al. 1980) and anti-inflammatory activity (Evans et al. 1991).

CBN has affinity for CB_1 receptors (Ki at CB1 = 308 nM) and signals as an agonist (Showalter et al. 1996). Further down the signal transduction cascade, it stimulates the binding of GTP-γ-S (Petitet et al. 1998), but with half the efficacy of THC; when CBN is added to THC, the effects are not significantly additive. CBN has a three-fold greater affinity for CB_2 receptors (Ki = 96 nM) (Showalter et al. 1996), thus it may affect cells of the immune system more than the central nervous system (Klein et al. 1998). CBN modulates thymocytes (Herring and Kaminski 1999) by attenuating the activity of the c-AMP response element-binding protein (CREB), nuclear factor κB (NF-κB), and interleukin-2 (IL-2). IL-2 is regulated by activator protein-1 (AP-1) transcription factor, a complex of c-Fos and c-Jun proteins (Foletta et al. 1998); CBN inhibits the expression of these proteins in splenocytes, via decreased activation of ERK MAP kinases (Faubert and Kaminski 2000).

Cannabichromene (CBC) is the fourth major cannabinoid, found predominantly in tropical *Cannabis* spp. strains (Figure 1). Until the mid-1970s, CBC was frequently misidentified as CBD, because CBC and CBD have nearly the

same retention times in gas chromatography. Like CBD, CBC decreases inflammation (Wirth et al. 1980) and provides analgesic effects (Davis and Hatoum 1983). CBC inhibits prostaglandin synthesis *in vitro*, but less potently than CBD or THC (Burstein et al. 1973). CBC exhibits strong antibacterial activity and mild antifungal activity, superior to THC and CBD in most instances (ElSohly et al. 1982). Unlike CBD, CBC has no effect on cytochrome P450 enzymes (Kapeghian et al. 1983), nor does it function as an anticonvulsant in rats (Davis and Hatoum 1983).

The molecular affinity of CBC for cannabinoid receptors has not been measured. In mice, CBC causes hypothermia, sedation, and synergizes the depressant effects of hexobarbital (Hatoum et al. 1981). CBC also sedates dogs and decreases muscular coordination in rats, but causes no cannabimimetic activity in monkeys and people (Turner et al. 1980). In rats, the co-administration of CBC with THC potentiates THC changes in heart rate, but does not potentiate THC's hypotensive effects (O'Neil et al. 1979). Co-administration of CBC lowers the LD_{50} dose of THC in mice (Hatoum et al. 1981).

Cannabigerol (CBG) is the biosynthetic precursor of CBC, CBD, and THC, and is present only in minor amounts (Figure 1). CBG has been called "inactive" when compared to THC, but CBG has slight affinity for CB_1 receptors, approximately the same as CBD (Devane et al. 1988). In rat brains, CBG inhibits the uptake of serotonin and norepinephrine, less effectively than CBD and THC, but CBG inhibits GABA uptake more effectively than CBD and THC (Banerjee et al. 1975). CBG acts as an analgesic (more potently than THC), it inhibits erythema (much more than THC), and it blocks lipoxygenase, again more effectively than THC (reviewed by Evans 1991).

CBG has antibacterial properties (Mechoulam and Gaoni 1965). Its activity against gram-positive bacteria, mycobacteria, and fungi is superior to that of THC, CBD, and CBC (ElSohly et al. 1982). CBG inhibits the growth of human oral epitheloid carcinoma cells (Baek et al. 1998).

Delta-8-THC (Δ^8-THC) is an isomer of delta-9-THC; it differs only by the location of the double bond in the cyclohexal "C" ring. The Ki of Δ^8-THC is 126 nM (Compton et al. 1993), and this loosely correlates with human studies, which show Δ^8-THC is less psychoactive than Δ^9-THC (Hollister 1974). The chemical stability of Δ^8-THC and its relative ease of synthesis compared to Δ^9-THC, have made Δ^8-THC the template for the development of two important synthetic derivatives, the extremely potent psychoactive CB_1 agonist, HU-210 (Mechoulam and Ben-Shabat 1999), and the non-psychoactive antiemetic and neuroprotectant, HU-211 (dexanabinol) (Achiron et al. 2000; Biegon and Joseph 1995; Gallily et al. 1997). Δ^8-THC was employed clinically in an important study (Abrahamov and Mechoulam 1995) in which 8 children with hematological malignancies were treated with the drug over the course of 8 months at a dose of 18 mg/m^2 to treat chemotherapy-associated

nausea and vomiting. Interestingly, not only was this agent uniformly effective as an antiemetic, but it was also free of psychoactive effects in this age range (2-13 years).

Tetrahydrocannabivarin (THCV) is a propyl analogue of Δ^9-THC, primarily appearing in *indica* and *afghanica* varieties of cannabis, such as hashish from Nepal (Merkus 1971), dagga from South Africa (Boucher et al. 1977), and in plants cultivated from seeds from Zambia (Pitts et al. 1992) (Figure 1). THCV is only 20-25% as psychoactive as Δ^9-THC (Hollister 1974). It has a quicker onset of action than Δ^9-THC (Gill et al. 1970), and is of briefer duration (Clarke 1998). THCV may be clinically effective in migraine treatment (Personal communication, HortaPharm, November 2000). Kubena and Barry (1972) suggested THCV synergizes the effects of THC, but did not hypothesize a mechanism. As a legal fine point, this analogue is not controlled in the Netherlands, and is not specified in the USA as a Schedule I drug, but would likely be considered illegal under the Controlled Substance Analogue Enforcement Act of 1986 (Public Law 99-570). THCV is of interest from a medical-legal standpoint in that is has been suggested as a biochemical marker of illicit cannabis use, since it is not a metabolite of Marinol® (synthetic THC) (ElSohly et al. 1999).

TERPENOIDS

The unique smell of cannabis does not arise from cannabinoids, but from over 100 terpenoid compounds (Turner et al. 1980). Terpenoids derive from repeating units of isoprene (C_5H_8), such as monoterpenoids (with C_{10} skeletons), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), and triterpenoids (C_{30}). The final structure of terpenoids ranges from simple linear chains to complex polycyclic molecules, and they may include alcohol, ether, aldehyde, ketone, or ester functional groups. These compounds are easily extracted from plant material by steam distillation or vaporization. This distillate is called the *essential oil* or *volatile oil* of the plant. A range of researchers cite different yields of essential oil from different types of cannabis: Martin et al. (1961) cited yields of 0.05-0.11% essential oil from fresh, green leaves and flowers of mixed male and female plants, from feral hemp growing in Canada. Nigram et al. (1965) yielded 0.1% essential oil from fresh, whole, male plants from Kashmir. Malingré et al. (1973) yielded 0.12% essential oil from fresh leaves of "strain X" obtained from birdseed in the Netherlands. Ross and ElSohly (1996) yielded 0.29% essential oil from fresh marijuana buds, reputed to be the Afghani variety "Skunk #1." Drying the plant material led to a loss of water content and net weight, concentrating the essential oil to 0.80% in buds that had been dried at room temperature for one week (Ross and ElSohly 1966).

Field-cultivated cannabis yields about 1.3 liter of essential oil per metric ton of freshly harvested plant material (Mediavilla and Steinemann 1997). Preventing pollination increases the yield of essential oil–18 l/ha in sinsemilla crops, versus 8 l/ha in pollinated crops (Meier and Mediavilla 1998). The composition of terpenoids varies between strains of cannabis (Mediavilla and Steinemann 1997), and varies between harvest dates (Meier and Mediavilla 1998).

Many terpenoids vaporize near the same temperature as THC, which boils at 157°C (see Figures 1-2). Terpenoids are lipophilic and permeate lipid membranes. Many cross the blood-brain barrier (BBB) after inhalation (Buchbauer et al. 1993; Nasel et al. 1994).

Meschler and Howlett (1999) discussed several mechanisms by which terpenoids modulate THC activity. For instance, terpenoids may bind to cannabinoid receptors. Thujone, from *Artemisia absinthium*, has a weak affinity for CB_1 receptors (Ki at CB_1 = 130,000 nM). Terpenoids might modulate the affinity of THC for its own receptor, by sequestering THC, by perturbing annular lipids surrounding the receptor, or by increasing the fluidity of neuronal membranes. Further downstream, terpenoids may alter the signal cascade by remodeling G-proteins. Terpenoids may alter the pharmacokinetics of THC by changing the BBB; cannabis extracts are known to cause a significant increase in BBB permeability (Agrawal et al. 1989). Terpenoids may also act on other receptors and neurotransmitters. Some terpenoids act as serotonin uptake inhibitors (as does Prozac®), enhance norepinephrine activity (as do tricyclic antidepressants), increase dopamine activity (as do monoamine oxidase inhibitors and bupropion), and augment GABA (as do baclofen and the benzodiazepines). Recently, strong serotonin activity at the 5-HT_{1A} and 5-HT_{2a} receptors has been demonstrated (Russo et al. 2000; Russo 2001) that may support synergistic contributions of terpenoids on cannabis-mediated pain and mood effects. Further studies are in progress to identify the most active terpenoid components responsible, and whether synergism of the components is demonstrable.

The essential oil of cannabis is traditionally employed as an anti-inflammatory in the respiratory and digestive tracts without known contraindications at physiological dosages (Franchomme and Pénoël 1990). The essential oil of black pepper, *Piper nigrum*, has a composition of terpenes that is qualitatively quite similar to that of cannabis (Lawless 1995). It has often been claimed anecdotally, that smoked cannabis may substitute for nicotine in attempts at smoking cessation. Aside from cannabinoid influences, current evidence supports this contention based on terpene content and its activity. A recent study has shown that inhalation of black pepper essential oil vapor significantly reduced withdrawal symptoms and anxiety in tobacco smokers (Rose and Behm 1994). Interestingly, the authors posited not a central biochemical mechanism,

FIGURE 1. Phytocannabinoids

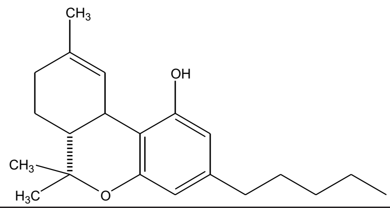
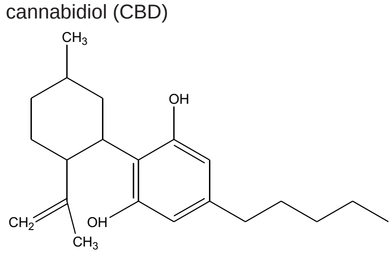
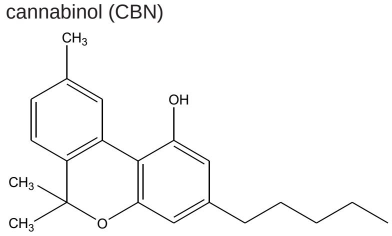
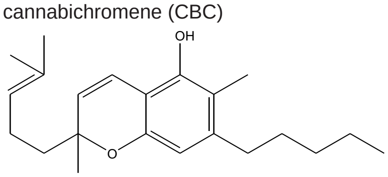
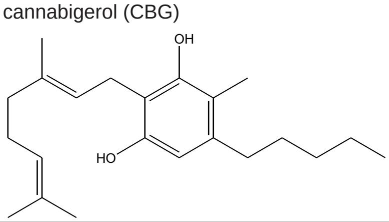
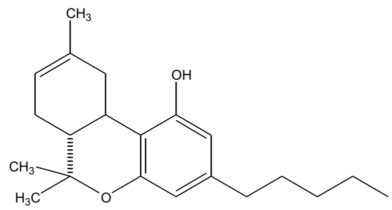
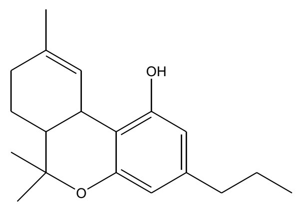
Structure*	**Concentration**† (% dry weight)	**Boiling Point °C**§	**Properties**
Δ-9-tetrahydrocannabinol (THC) 	0.1-25%	157	Euphoriant Analgesic Antiinflammatory Antioxidant Antiemetic
cannabidiol (CBD) 	0.1-2.89%	160-180	Anxiolytic Analgesic Antipsychotic Antiinflammatory Antioxidant Antispasmodic
cannabinol (CBN) 	0.0-1.6%	185	Oxidation breakdown product Sedative Antibiotic
cannabichromene (CBC) 	0.0-0.65%	220	Antiinflammatory Antibiotic Antifungal
cannabigerol (CBG) 	0.03-1.15%	MP 52	Antiinflammatory Antibiotic Antifungal

FIGURE 1 (continued)

Structure*	**Concentration†** (% dry weight)	**Boiling Point °C§**	**Properties**
Δ-8-tetrahydrocannabinol (Δ-8-THC) 	0.0-0.1%	175-178	Resembles Δ-9-THC Less psychoactive More stable Antiemetic
tetrahydrocannabivarin (THCV) 	0.0-1.36%	< 220	Analgesic Euphoriant

*Structures of constituents obtained from Bissett and Wichtl 1994; British Medical Association 1997; Buckingham 1992; Iversen 2000; Tisserand and Balacs 1995; Turner et al. 1980.

†Concentrations of constituents (v/w or w/w) were calculated from various sources. Cannabinoid concentrations (presented as a range, including cannabinoids and cannabinoidic acids) were primarily obtained from Small, 1979; Veszki et al., 1980; Fournier et al., 1987; and Pitts et al., 1992. Terpenoid data (presented as maximum values) were calculated from Ross and El Sohly, 1996; and Mediavilla and Steinemann, 1997. Flavonoid data came from Paris et al., 1976; and Barrett et al., 1986.

§Boiling/melting points (MP) recorded at atmospheric pressure (760 mmHg) unless otherise noted; values obtained from various sources, primarily Buckingham, 1992; Guenther, 1948; Parry, 1918; and Mechoulam (personal communication, April 2001).

but rather a peripheral one assuming physical cues of bronchial sensation as operative in the origin of the benefit. The true scope of the essential oil benefits in this context may be quite a bit broader.

Pate (1994), McPartland (1997), and McPartland, Clarke and Watson (2000), have reviewed the pesticidal properties of cannabis attributable to its terpenoid content. The essential oil of *Eugenia dysenterica* was recently demonstrated to have significant inhibitory effects on *Cryptococcus neoformans* strains isolated from HIV patients with cryptococcal meningitis (Costa et al. 2000). Key components of that oil were common to cannabis: β-caryophyllene, α-humulene, α-terpineol, and limonene.

Additionally, monoterpenes such as those abundant in cannabis resin have been suggested to: (1) inhibit cholesterol synthesis, (2) promote hepatic en-

FIGURE 2. Terpenoid essential oil components of cannabis.

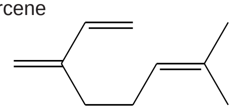
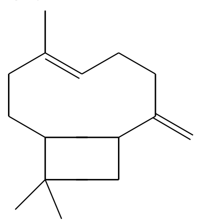
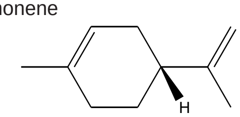
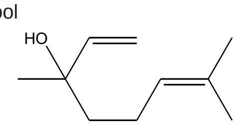
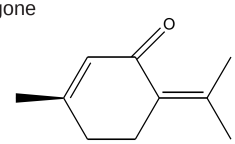
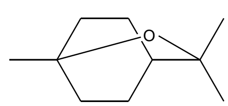
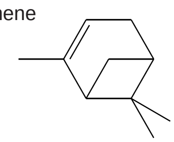
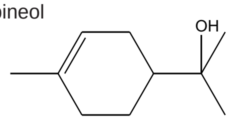
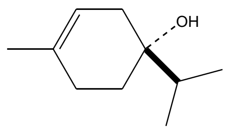
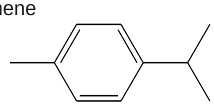
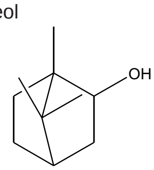
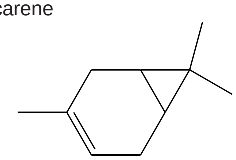
Cannabis Constituent Structure*	**Concentration**†	**Boiling Point °C**§	**Properties**
β-myrcene 	0.47%	166-168	Analgesic Antiinflammatory Antibiotic Antimutagenic
β-caryophyllene 	0.05%	119	Antiinflammatory Cytoprotective (gastric mucosa) Antimalarial
d-limonene 	0.14%	177	Cannabinoid agonist? Immune potentiator Antidepressant Antimutagenic
linalool 	0.002%	198	Sedative Antidepressant Anxiolytic Immune potentiator
pulegone 	0.001%	224	Memory booster? AChE inhibitor Sedative Antipyretic
1,8-cineole (eucalyptol) 	> 0.001%	176	AChE inhibitor Increases cerebral blood flow Stimulant Antibiotic Antiviral Antiinflammatory Antinociceptive
α-pinene 	0.04%	156	Antiinflammatory Bronchodilator Stimulant Antibiotic Antineoplastic AChE inhibitor

FIGURE 2 (continued)

Cannabis Constituent Structure*	Concentration[†]	Boiling Point °C[§]	Properties
α-terpineol 	0.02%	217-218	Sedative Antibiotic AChE inhibitor Antioxidant Antimalarial
terpineol-4-ol 	0.0004%	209	AChE inhibitor Antibiotic
p-cymene 	0.0004%	177	Antibiotic Anticandidal AChE inhibitor
borneol 	0.008%	210	Antibiotic
Δ-3-carene 	0.004%	168	Antiinflammatory

zyme activity to detoxify carcinogens, (3) stimulate apoptosis in cells with damaged DNA, and (4) inhibit protein isoprenylation implicated in malignant deterioration (Jones 1999).

Myrcene, specifically β-myrcene, a noncyclic monoterpene, is the most abundant terpenoid produced by cannabis (Ross and ElSohly 1996; Mediavilla and Steinemann 1997). It also occurs in high concentrations in hops (*Humulus lupulus*) and lemongrass (*Cymbopogon citratus*). Myrcene is a potent analgesic, acting at central sites that are antagonized by naloxone (Rao et al. 1990). Myrcene also works via a peripheral mechanism shared by CBD, CBG, and CBC–by blocking the inflammatory activity of prostaglandin E_2 (Lorenzetti et al. 1991). This activity is expressed by other terpenoids in cannabis smoke,

such as carvacrol, which is more potent than THC or CBG (Burstein et al. 1975). The activity of many terpenoids may be cumulative: unfractionated cannabis essential oil exhibits greater antiinflammatory activity than its individual constituents, suggesting synergy (Evans et al. 1987).

Myrcene also synergizes the antibiotic potency of other essential oil components, against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa*, and a specific strain of *Escherichia coli* (Onawunmi et al. 1984). Myrcene inhibits cytochrome P450 2B1, an enzyme implicated in the metabolic activation of promutagens (De Oliveira et al. 1997). Aflatoxin B_1 is a promutagen produced by *Aspergillus flavus* and *Aspergillus parasiticus*, two fungal contaminants of moldy marijuana (reviewed by McPartland and Pruitt 1997). After aflatoxin B_1 is metabolized by P450 2B1, it becomes extremely hepatocarcinogenic. Myrcene blocks this metabolism, as do other terpenoids in cannabis, including limonene, α-pinene, α-terpinene, and citronellal (De Oliveira et al. 1997).

β-Caryophyllene is the most common sesquiterpenoid in cannabis (Mediavilla and Steinemann 1997). It is the main component of copaiba balsam, from *Copaifera* spp. (Lawless 1995), which is a popular oral and topical anti-inflammatory agent in Brazil (Basile et al. 1988). The latter authors were able to demonstrate anti-inflammatory effects of the oleoresin in rats comparable to phenylbutazone, in reduction of granuloma formation. A decreased vascular permeability to injected histamine was also observed.

A gastric cytoprotective effect of β-caryophyllene was demonstrated in rats against challenge with absolute ethanol and hydrochloric acid (Tambe et al. 1996). This benefit was noted without influence on gastric acid or pepsin secretion. The authors suggested this agent as clinically safe, and potentially useful. Campbell et al. (1997) have demonstrated a moderate antimalarial effect against two strains of *Plasmodium falciparum* by an essential oil rich in β-caryophyllene and α-terpineol.

Limonene is a monocyclic monoterpenoid and a major constituent of citrus rinds (Tisserand and Balacs 1995). It finds extensive use as a solvent and in the perfumery and flavor industries. Because of limonene's widespread occurrence and application, its biological activity is well known. Limonene is highly absorbed by inhalation and quickly appears in the bloodstream (Falk-Flilipsson et al. 1993). According to Ross and ElSohly (1996), limonene is the second most common terpenoid in an unidentified cultivar of cannabis.

Limonene may have a low-affinity interaction with cannabinoid receptors (Meschler and Howlett 1999). Studies of long-term inhalation of lemon fragrance (predominately limonene) have demonstrated inhibition of thymic involution in stress-induced immunosuppression in mice (Ortiz de Urbina et al. 1989).

Limonene was the primary component of the essential oil mixture employed by Komori et al. (1995), in their clinical study of immune function and depressive states in humans. The key result of this experiment was the ability to markedly reduce the dosage of, or even eliminate the need for, synthetic antidepressant drugs.

As mentioned in the myrcene section, limonene protects against aflatoxin B_1-induced cancer by inhibiting the hepatic metabolism of the promutagen to its active form. Limonene also blocks this process at two earlier steps by inhibiting the growth of *Aspergillus* fungi and inhibiting their production of aflatoxins (Greene-McDowelle et al. 1999). Limonene and other terpenoids suppress the growth of many species of fungi and bacteria, demonstrated in hundreds of published studies (reviewed by McPartland 1997).

Limonene blocks the carcinogenesis induced by benz[α]anthracene (Crowell 1999), a component of the "tar" generated by the combustion of herbal cannabis. Thus, this terpenoid may reduce the harm caused by inhaling cannabis smoke. Limonene blocks carcinogenesis by multiple mechanisms. It detoxifies carcinogens by inducing Phase II carcinogen-metabolizing enzymes (Crowell 1999). It selectively inhibits the isoprenylation of Ras proteins, thus blocking the action of mutant *ras* oncogenes (Hardcastle et al. 1999). It induces redifferentiation of cancer cells (by enhancing expression of transforming growth factor β1 and growth factor II receptors), and it induces apoptosis of cancer cells (Crowell 1999). Orally administered limonene is currently undergoing Phase II clinical trials in the treatment of breast cancer (Vigushin et al. 1998); it also protects against lung, liver, colon, pancreas, and skin cancers (Vigushin et al. 1998; Crowell 1999; Setzer et al. 1999).

Linalool is a noncyclic monoterpenoid, commonly extracted from lavender (*Lavandula* spp.), rose (*Rosa* spp.), and neroli oil (from *Citrus aurantium*). It usually constitutes 5% or less of cannabis essential oil (Ross and ElSohly 1996). Linalool nevertheless exhibits strong biological activity. Buchbauer et al. (1993) assayed the sedative effects of over 40 terpenoids upon *inhalation* by mice; linalool was the most powerful, reducing mouse motility 73% after 1 hour of inhalation. The study demonstrated that other terpenoids found in cannabis, such as citronellol and α-terpineol, are also deeply sedating upon inhalation, even in low concentrations. Furthermore, combinations of these terpenoids (e.g., neroli oil) are synergistic in their sedative effects. These terpenoids may mitigate the anxiety provoked by pure THC. Inhalation of such terpenoids also provides antidepressant effects (Komori et al. 1995).

Reducing anxiety and depression will improve immune function via the neuroendocrine system, by damping down the hypothalamic-pituitary-adrenal (HPA) axis. Hence, inhalation of terpenoids reduces the secretion of HPA stress hormones (e.g., corticosterone), and normalizes CD4-CD8 ratios (Komori et al. 1995). By a similar mechanism, terpenoids in *Ginkgo biloba* inhibit

corticosterone secretion by attenuating corticotropin-releasing factor (CRF) expression (Marcihac et al. 1998). CRF not only induces corticosterone secretion via the HPA axis, it is also associated with anxiety. Rodríguez de Fonseca et al. (1996) showed that the psychoactive cannabinoid HU-210 caused a release of CRF. Thus, the terpenoids act synergistically with non-psychoactive CBD, which may decrease CRF by inhibiting IFN-γ (Malfait et al. 2000).

Pulegone, a monocyclic monoterpenoid, is a minor constituent of cannabis (Turner et al. 1980). Higher concentrations of pulegone are found in rosemary (*Rosmarinus officinalis*), "the herb of remembrance." Pulegone may alleviate a major side effect of THC–loss of short-term memory consolidation. THC causes acetylcholine (ACh) deficits in the hippocampus. Hippocampal ACh deficits are also seen in people with Alzheimer's disease. Alzheimer's patients can be treated with tacrine (Cognex®), a drug that increases ACh activity by inhibiting acetylcholinesterase (AChE). Indeed, tacrine has blocked THC-induced memory loss behavior in rats. Pulegone exhibits the same activity as tacrine, that of AChE inhibition (Miyazawa et al. 1997). Other terpenoids in cannabis also provide AChE inhibition, including limonene, limonene oxide, α-terpinene, γ-terpinene, terpinen-4-ol, carvacrol, l-and d-carvone, 1,8-cineole, *p*-cymene, fenchone, and pulegone-1,2-epoxide (Perry et al. 1996; McPartland and Pruitt 1999). The beneficial effects of AChE inhibitors, however, are decreased in individuals carrying the E4 subtype of the apolipoprotein E gene, ApoE E4 (Poirier et al. 1995). Pulegone has also demonstrated significant sedative and antipyretic properties in a study in rats (Ortiz de Urbina et al. 1989).

1,8-Cineole, a bicyclic monoterpenoid, is a minor constituent of cannabis and the major aromatic found in *Eucalyptus* species. Studies show the inhalation of 1,8-cineole increases cerebral blood flow and enhances cortical activity (Nasel et al. 1994). Brain function is enhanced by administering terpenoids that improve cerebral blood flow, much as the ginkgolides in *Ginkgo biloba* (Russo 2000). Similarly, cerebral blood flow increases after inhaling cannabis smoke, and this increase is *not* related to plasma levels of THC (Mathew and Wilson 1993).

A stimulatory effect on rat locomotion was demonstrated employing a 1,8-cineole-rich essential oil of rosemary with a terpene profile similar to that of cannabis (Kovar et al. 1987). Blood levels correlated with the degree of stimulation observed. Antinociceptive and anti-inflammatory effects of 1,8-cineole were demonstrated at high doses in rats, using carrageenan rat paw and cotton pellet-induced granuloma models (Santos and Rao 2000). An analgesic effect of an essential oil was demonstrated in another animal study, and correlated with the 1,8-cineole concentration (Aydin et al. 1999).

1,8-Cineole demonstrated antibacterial activity against *Bacillus subtilis*, and antifungal properties against *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, and *Candida albicans* (Hammerschmidt et al. 1993). In subse-

quent assays, this essential oil component was cidal against *Candida albicans* and *Escherichia coli*, and bacteriostatic against *Staphylococcus aureus* (Carson and Riley 1995). In a rat study, 1,8-cineole prevented the sexual transmission of *Herpes simplex* virus type 2 (HSV-2). HSV-2 is a frequently comorbid condition with HIV, and its prevention has been suggested as one method of lowering HIV transmission risks (Gwanzura et al. 1998).

Perry et al. (2000) demonstrated that 1,8-cineole was an inhibitor of human erythrocyte acetylcholinesterase, but that an essential oil of *Salvia lavandulaefolia* containing 1,8-cineole and other terpenoids produced a synergistic inhibition of acetylcholinesterase that suggested utility in the clinical treatment of Alzheimer's disease. A similar mechanism may operate in cannabis essential oil with the same components.

α-Pinene, a bicyclic monoterpenoid, was effective in prevention of acute inflammation in a carrageenan-induced plantar edema model (Gil et al. 1989). A pharmacokinetics study of inhaled α-pinene in humans demonstrated 60% uptake, and a relative bronchodilation effect (Falk et al. 1990). After 1 hour of inhalation, α-pinene produced a 13.8% increase in mouse motility measures (Buchbauer et al. 1993). α-Pinene has inhibited acetylcholinesterase in a variety of assays (Perry et al. 1996; McPartland and Pruitt 1999), suggesting utility in the clinical treatment of Alzheimer's disease. The antibiotic properties of α-pinene, α-terpineol, and terpinen-4-ol have been demonstrated against *Staphylococcus aureus, S. epidermidis* and *Propionibacterium acnes* (Raman et al. 1995). α-Pinene and its isomer β-pinene were both cytotoxic *in vitro* against Hep-G2 (human hepatocellular carcinoma) and Sk-Mel-28 (human melanoma) tumor cell lines (Setzer et al. 1999).

α-Terpineol, terpinen-4-ol, and 4-terpineol are three closely related monoterpenoids. Inhalation of α-terpineol reduced mouse motility 45% (Buchbauer et al. 1993). Burits and Bucar (2000) demonstrated that 4-terpineol exhibits "respectable" radical scavenging and antioxidant properties. Terpinen-4-ol, α-terpineol, and α-pinene demonstrated dose-dependent antibiotic properties against *Staphylococcus aureus, S. epidermidis* and *Propionibacterium acnes* (Raman et al. 1995). Similar studies have demonstrated antimicrobial activity against a wide range of pathogenic organisms, excluding *Pseudomonas* (Carson and Riley 1995). Campbell et al. (1997) have demonstrated a moderate antimalarial effect against two strains of *Plasmodium falciparum* by an essential oil with major α-terpineol and α-caryophyllene components.

Cymene, or *p*-cymene, a monoterpenoid, is active against *Bacterioides fragilis, Candida albicans*, and *Clostridium perfringens* (Carson and Riley 1995).

Borneol, a bicyclic monoterpenoid, was tested in walnut oil as an external treatment for purulent otitis media (Liu 1990), where it proved to be 98% effective ($P < 0.001$), to a greater degree than neomycin, and without toxicity.

Δ^3-Carene, a bicyclic monoterpenoid, was effective in prevention of acute inflammation in a carrageenan-induced plantar edema model (Gil et al. 1989).

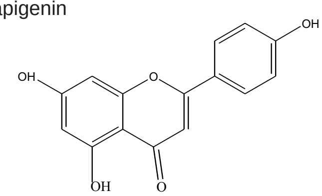
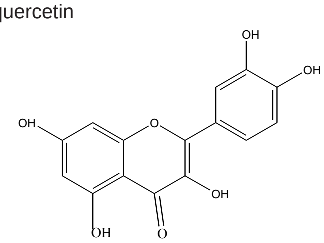
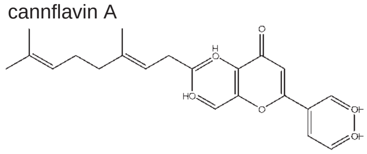
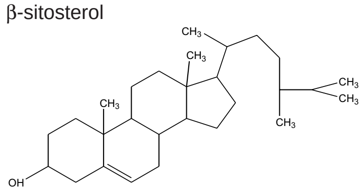
FLAVONOIDS

Flavonoids are aromatic, polycyclic phenols. Cannabis produces about 20 of these compounds, as free flavonoids and conjugated glycosides (Turner et al. 1980). Paris et al. (1976) estimated that cannabis leaves consist of 1% flavonoids. Some flavonoids are volatile, lipophilic, permeate membranes, and apparently retain pharmacological activity in cannabis smoke (Sauer et al. 1983). Flavonoids may modulate the pharmacokinetics of THC, via a mechanism shared by CBD, the inhibition of P450 3A11 and P450 3A4 enzymes. Naringenin, a flavonoid in grapefruit juice, also inhibits these enzymes, thus blocking the metabolism of cyclosporine, caffeine, benzodiazepines, and calcium antagonists (Fuhr 1998). Two related enzymes, P450 3A4 and P450 1A1, metabolize environmental toxins from procarcinogens to their activated forms. Thus, P450-suppressing compounds serve as chemoprotective agents, shielding healthy cells from the activation of benzo[α]pyrene and aflatoxin B_1 (Offord et al. 1997), which are two procarcinogens potentially found in cannabis smoke (McPartland and Pruitt 1997).

Apigenin is a flavone found in nearly all vascular plants (Figure 3). It exerts a wide range of biological effects, including many properties shared by terpenoids and cannabinoids. Apigenin is the primary anxiolytic agent found in chamomile, *Matricaria recutita*, (reviewed in Russo 2000). It selectively binds with high affinity to central benzodiazepine receptors, which are located in α- and β-subunits of $GABA_A$ receptors (Salgueiro et al. 1997); this anxiolytic activity is not associated with the unwanted side effects caused by synthetic benzodiazepines, such as muscular relaxation, amnesia, and sedation.

Apigenin inhibits the production of tumor necrosis factor-alpha (TNF-α), a cytokine primarily expressed by monocytes and macrophages (Gerritsen et al. 1995). TNF-α induces and maintains inflammation, a pathological condition in rheumatoid arthritis and multiple sclerosis. THC decreases TNF-α, probably by a nonreceptor-mediated mechanism (Burnette-Curley and Cabral 1995), although one study suggested THC might induce TNF-α (Shivers et al. 1994). Either way, apigenin provides beneficial suppression of TNF-α, whether in concert with THC or counteracting THC.

FIGURE 3. Flavonoid and phytosterol components of cannabis.

Cannabis Constituent Structure*	**Concentration†**	**Boiling Point °C§**	**Properties**
apigenin 	> 0.1%	178	Anxiolytic Antiinflammatory Estrogenic
quercetin 	> 0.1%	250	Antioxidant Antimutagenic Antiviral Antineoplastic
cannflavin A 	0.02%	182	COX inhibitor LO inhibitor
β-sitosterol 	?	134	Antiinflammatory 5-α-reductase inhibitor

Apigenin and other flavonoids interact with estrogen receptors, and appear to be the primary estrogenic agents in cannabis smoke (Sauer et al. 1983). Although apigenin has a high affinity for estrogen receptors (especially β-estrogen receptors), it has low estrogenic activity; apigenin actually inhibits estradiol-induced proliferation of breast cancer cells (Wang and Kurzer 1998).

Quercetin is a flavonol found in nearly all vascular plants, including cannabis (Turner et al. 1980). Quercetin is a potent antioxidant; by some measures more potent than ascorbic acid, α-tocopherol, and BHT (Gadow et al. 1997). Combinations of quercetin and other antioxidants work synergistically (Hud-

son and Mahgoub 1981). The antioxidant potential of quercetin and other flavonoids should be tested against CBD, another potent antioxidant (Hampson et al. 1998). Perhaps flavonoids can induce chemical reduction of CBD, effectively recycling CBD as an antioxidant. Flavonoids block free radical formation at several steps: by scavenging superoxide anions (in both enzymatic and non-enzymatic systems), by quenching intermediate peroxyl and alkoxyl radicals, and by chelating iron ions, which catalyze many Fenton reactions leading to free radical formation (Musonda and Chipman 1998).

Free radicals activate NF-κB, a transcription factor protein that induces the expression of oncogenes, inflammation, and apoptosis. Quercetin arrests the formation of NF-κB, by blocking the PKC-induced phosphorylation of an inhibitory subunit of NF-κB called IκB (Musonda and Chipman 1998), consequently quercetin hinders carcinogenesis and inflammatory diseases. NF-κB also plays a role in the activation of HIV-1 (Greenspan 1993), so quercetin may hinder the replication of that virus. In a similar fashion, silymarin (a flavonoid produced by milk thistle, *Silybum marianum*) impedes NF-κB-induced replication of the hepatitis C virus, and thus inhibits hepatic carcinoma (McPartland 1996). These flavonoids may synergize with CBN, which also downregulates NF-κB (Herring and Kaminski 1999), thereby counteracting the effects of THC, which may increase NF-κB activity (Daaka et al. 1997).

Cannflavin A is one of a pair of prenylated flavones apparently unique to cannabis (Barrett et al. 1986). The yield of cannflavin A is 0.02% of dry herb. This compound is a potent inhibitor of prostaglandin E_2 in human rheumatoid synovial cells, with an IC_{50} of 31 ng/ml, about 30 times more potent than aspirin in that system (Barrett et al. 1986). Cannflavin A inhibits cyclooxygenase (COX) enzymes and lipoxygenase (LO) enzymes more potently than THC (Evans et al. 1987). However, these assays were done with alcohol-extracted cannflavin; we question whether cannflavin is sufficiently volatile. Other phenols related to flavonoids are volatile and apparently retain pharmacological activity in cannabis smoke, such as eugenol and *p*-vinylphenol (Burstein et al. 1976).

β-Sitosterol was demonstrated in significant concentrations in the red oil extract of cannabis (Fenselau and Hermann 1972). In animal assays, this phytosterol reduced acute inflammation 65% and chronic edema 40.6% (Gomez et al. 1999). This agent has been the subject of most interest as the active ingredient of *Serenoa repens*, the saw palmetto, and *Urtica dioica*, the nettle, wherein β-sitosterol acts as a 5-α-reductase inhibitor. In numerous trials (Wilt et al. 1998; McPartland and Pruitt 2000), standardized extracts of saw palmetto have proven equivalent or superior to finasteride in treatment of benign prostatic hyperplasia.

CONCLUSIONS

Does the body absorb non-cannabinoids in physiologically relevant concentrations? In the absence of experimental data, we can estimate, using limonene as an example of AChE inhibition. According to Ross and ElSohly (1996), fresh, female flowering tops consist of 0.29% essential oil. Air drying of female flowering tops decreases their moisture content (MC) from approximately 85% MC to 15% MC, with a concomitant loss in water weight (McPartland and Pruitt 1997). Although some essential oil is volatilized and lost in the drying process, the remaining terpenoids become concentrated. The concentration of essential oil in air-dried cannabis is 0.8%, and limonene consists of 17.2% of the essential oil (Ross and ElSohly 1996). Thus, air-dried cannabis consists of 0.14% limonene; therefore a 500 mg cannabis cigarette (which is half the size of a standard tobacco cigarette) would contain 0.7 mg limonene. If we assume the systemic bioavailability of limonene from smoking cannabis is 18%, the same as THC (Ohlsson et al. 1980), then 0.13 mg would be absorbed. Distributing this dose evenly in the total body water of a 70 kg man, without metabolism or sequestration, would produce a maximum tissue concentration of 1.3 μM. This concentration is an order of magnitude below the IC_{50} concentration of limonene's inhibition of AChE (Miyazawa et al. 1997). Hence, limonene *must* synergize with other AChE inhibitors in order to be effective.

Vaporizer technology may improve the bioavailability of limonene and other compounds, which volatilize around the same temperature as THC (see Figures 1-3). Vaporizers are smoking apparati that heat cannabis to 185°C (365°F), which vaporizes THC but is below the ignition point of combustible plant material. Vaporized cannabis emits a thin gray vapor, whereas combusted cannabis produces a thick smoke. Thus, vaporizers deliver a better cannabinoid-to-tar ratio than cigarettes or water pipes (Gieringer 1996). In a recent study, traces of THC were vaporized at temperatures as low as 140°C (284°F) and the majority of THC vaporized by 185°C (365°F); benzene and other carcinogenic vapors did not appear until 200°C (392°F), and cannabis combustion occurred around 230°C (446°F) (Gieringer 2001).

Concerning bioavailability, it should be mentioned that cannabis compounds need not be absorbed systemically through the lungs to produce CNS activity. Inhaled compounds may reach receptors in the olfactory bulb, sending mood-altering messages via olfactory nerves directly to the limbic region and hippocampus. This route may be responsible for some sedative effects of terpenoids upon inhalation (Buchbauer et al. 1993).

The paucity of research concerning non-THC synergists in cannabis is periodically criticized (Mechoulam et al. 1972; McPartland and Pruitt 1999; Russo 2000). We have highlighted several cannabinoids, terpenoids, and flavonoids

that deserve further attention regarding their contributions to the effects of clinical cannabis. Most of the data we present here is based on *in vitro* experiments or animal studies. Clearly the next step should involve human clinical trials of each constituent, alone, or in combination with THC, or combined with a cocktail of cannabis compounds.

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Harm Reduction Associated with Inhalation and Oral Administration of Cannabis and THC

Franjo Grotenhermen

SUMMARY. Inhalation of carcinogenic combustion products associated with smoking is generally regarded as the major health hazard in connection with the medical use of cannabis products. Strategies to reduce respiratory and other adverse events resulting from this common practice include relinquishment of inhalation and replacement by other routes of administration, the use of plants with a high THC content allowing reduction of the amount of smoked plant material, usage of inhalation devices that improve the ratio of THC and tar, and avoidance of the Valsalva maneuver that may cause spontaneous pneumothorax. The major risk associated with oral cannabis use is accidental overdosage, especially in inexperienced users that can be avoided by appropriate dosing procedures. A combination of oral use and inhalation may be meaningful in several indications, decreasing the specific risks of both routes. Preliminary studies using rectal, sublingual and transdermal routes indicate that these alternatives to the two most common forms of ingestion may be utilized medicinally in the future, further reducing the possible risks associated with the administration of cannabis or single cannabinoids. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

Franjo Grotenhermen is affiliated with nova-Institut, Goldenbergstraße 2, D-50354 Hürth, Germany (E-mail: franjo-grotenhermen@nova-institut.de).

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INTRODUCTION

Major objections to the use of crude cannabis products medicinally are often based not on properties of the natural herb itself, but on the possible adverse health effects resulting from the most prevalent form of application in recreational use: smoking a marijuana cigarette or pipe (Joy et al. 1999; Tashkin 2001). The major advantages of inhalation of cannabis or THC are rapid onset of action and flexible dose titration, making this route of administration very attractive to medical users. Dronabinol is a synonym for the natural (−)-trans isomer of delta-9-THC (the pharmacological most active isomer of delta-9-THC that is present in the cannabis plant) when synthesized and manufactured as Marinol . The oral route is more prone to improper dosing, resulting in unwanted side effects due to overdosage. However, this route may be advantageous if a long duration of drug action is desired. Harm reduction techniques are intended to minimize the health risks associated with different routes of application while maintaining the specific pharmacokinetic advantages.

PHARMACOKINETICS

Depending on method of administration, there are significant differences in absorption and metabolism of THC, attendant effects, time until onset of action, and duration (Table 1).

Pulmonary absorption of cannabis results in maximum THC concentration within about five minutes. THC is detectable in plasma only seconds after the first inhalation. Psychotropic effects commence within seconds to minutes, are maximal after 30 min, and last about 2-3 h. Certain effects may last longer. Thus, Meinck et al. (1989) measured an improvement of some spasticity parameters for more than 12 hours after smoking a cannabis cigarette.

Agurell et al. (1986) noted that only about 20% of the THC present in a marijuana cigarette was absorbed via mainstream smoke when a group of cannabis users inhale in their customary fashion. Thus, most of the THC is lost in side-stream smoke. Effectiveness may be even lower in inexperienced users with a bioavailability below 10%. In experienced users the highest systemic bioavailability measured was 56% (Agurell et al. 1986). Davis et al. (1984) have analyzed smoking characteristics of marijuana cigarettes with a smoking

TABLE 1. Pharmacokinetic comparison of THC application to humans via intravenous, respiratory and oral routes. (Agurell et al. 1986, Azorlosa et al. 1992, Frytak et al. 1984, Wall et al. 1983, Ohlsson et al. 1980, Perez-Reyes et al. 1981, Perez-Reyes et al. 1973)

Parameter	**Intravenous**	**Inhaled**	**Oral (lipophilic vehicle)**
Absorption	100%	10-30 (up to 50)%	> 95%
Systemic bioavailability	100%	10-30 (up to 50)%	10-20%
Psychotropic threshold per kg body weight	0.02 mg/kg	0.06-0.1 mg/kg	0.2-0.3 mg/kg
Psychotropic threshold per individual	1 mg	3-6 mg	ca. 10-20 mg
Maximum plasma concentration at the psychotropic threshold	30-50 ng/ml	30-50 ng/ml	3-5 ng/ml
Dose producing marked intoxication*	2-4 mg	10-20 (up to 50) mg	30-40 (up to 90) mg
Onset of action	within seconds	within seconds	30-60 (up to 120) min
Duration of action**	2-3 (up to 4) h	2-3 (up to 4) h	5-8 (up to 12) h

* Doses producing a marked intoxication vary according to duration of therapy. Longer use may result in the development of tolerance, and higher doses are needed to achieve the similar effects.
** Duration of action varies according to examined effect and especially with oral use according to dose.

machine. When the whole cigarette was consumed in a single puff yielding little side stream smoke, 69% of the THC was preserved in the mainstream smoke, with about 30% lost due to pyrolysis. Smoking a pipe that produces little side stream smoke may also result in high effectiveness, with an average of 45% of THC transferred via the mainstream smoke (Agurell et al. 1986).

After oral ingestion of cannabis, absorption is slow and erratic. Onset of effects is delayed for 30-90 min. Maximum plasma concentrations following 10-15 mg oral THC in sesame oil were noted after 1.75-7 h (Agurell et al. 1986; Brenneisen et al. 1996), usually peaking after about 2 hours. More than one plasma peak may also occur. Compared to inhalation, effects after oral ingestion last longer and fade away more slowly, over 5-8 h, or even longer with very high doses. Duration of action also depends on measured parameters.

Intestinal absorption of THC is increased by application in a lipophilic vehicle. Ohlsson et al. (1980) reported a systemic bioavailability of 6% (3%) after ingestion of THC in a chocolate cookie. Oral bioavailability was of the order of 10-20% after ingestion of THC in oil capsules (Wall et al. 1983). Therefore, cream or milk can be added to a marijuana tea, or a recipe with plenty of butter

may be used if the drug is baked in confections. ^{9}-THC may be degraded by the acid of the stomach and in the gut. Several competing reactions occur at low pH, among them isomerization to ^{8}-THC and protonation of the oxygen in the pyran ring, causing ring cleavage to substituted cannabidiols (Agurell et al. 1986). In lipophilic vehicles, such as in the case of Marinol capsules, where THC is dissolved in sesame oil, at least 95% of THC is absorbed from the gastrointestinal tract (Wall et al. 1983). Due to an extensive first-pass liver metabolism and pre-systemic elimination in the gut, with oral application systemic bioavailability is only 10-20% (Agurell et al. 1986).

In the cannabis plant, about 95% of ^{9}-THC is present as one of two pharmacologically inactive acid forms, the ^{9}-THC carboxylic acids (THCA) (Turner et al. 1980). Natural cannabinoids must be decarboxylated before ingestion, since the corresponding neutral phenolic forms of THC produce most biological effects. The simplest and fastest way to achieve this is through heating (smoking, baking, cooking). Neutral phenols are responsible for the known pharmacological effects of dronabinol. Five minutes of heating to 200-210°C has been determined as the optimal condition for complete decarboxylation of THCA without oxidation to cannabinol (Brenneisen 1984). In cannabis smoking, where temperatures of 600°C are achieved, only a few seconds of combustion are apparently sufficient for decarboxylation.

INHALATION OR ORAL APPLICATION

Cannabis and THC can both be administered by various routes. Inhalation and oral use are the most frequent ways to ingest the drug, each demonstrating particular advantages and disadvantages. The advantage of oral intake is its more constant and prolonged activity, for example, in the prevention of nocturnal spasms in multiple sclerosis, or decreasing intraocular pressure for several hours. Its disadvantage is possible overdosage, especially with cannabis preparations of unknown THC content.

The major advantages of inhalation are fast onset of action and easy titration of dose. These are preferable in acute disorders that demand a fast effect, such as rapidly treating a migraine attack, or combating breakthrough pain. Inhalation is also superior to ingestion by mouth in nausea and vomiting, where it may be difficult to take pills or other oral preparations. The disadvantage of smoking is potential damage to the respiratory tract.

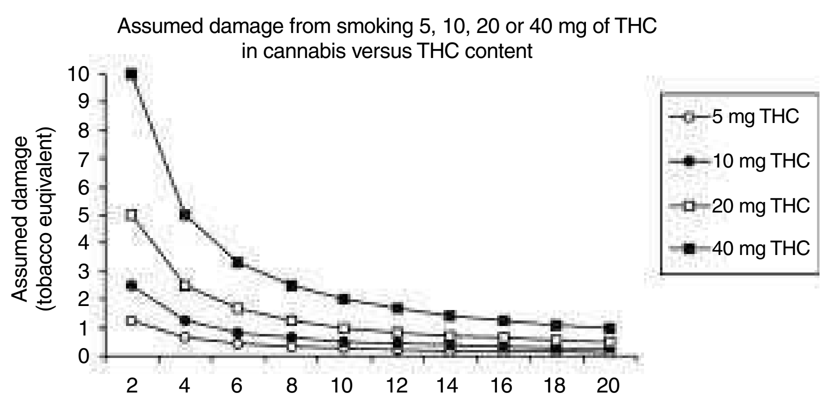
RISKS OF SMOKING

More than 200 combustion products have been found in marijuana smoke (Sparacino et al. 1990), and many are known to be toxic to tissues of the respi-

ratory and upper intestinal tract. Aside from the nicotine content, cannabis smoke is qualitatively similar to that of tobacco (Tashkin 2001). Benzo[ ]anthracene and benzo[ ]pyrene, two highly procarcinogenic polycyclic aromatic hydrocarbons (PAHs) are present in 25-75% higher concentrations in the tar from cannabis as compared to tobacco (Lee et al. 1976). The deposition of PAHs is amplified approximately 4 times by a higher tar yield of unfiltered marijuana cigarettes compared to filter-tipped tobacco cigarettes, and a longer breathholding time with marijuana (Wu et al. 1988). A 4-fold longer breathholding results in a 40% greater deposition of tar in the respiratory tract (Wu et al. 1988).

Whether this higher tar yield from cannabis smoke leads to a fourfold stronger damage of the mucosa compared to smoking the same amount of tobacco is unclear. A fourfold increase may be regarded as the worst-case scenario, whereby smoking half a cannabis cigarette (about 0.4 grams of cannabis) would damage the mucosa to a similar degree as two tobacco cigarettes (see Figure 1). Histopathological alterations of the airways associated with smoking may lead to chronic bronchitis and, hypothetically, eventually to chronic

FIGURE 1. Assumed risk associated with smoking herbal cannabis vs. THC content (as % of the dried plant material) corresponding to that caused by tobacco cigarettes. The worst-case scenario is assumed, that smoking a certain amount of cannabis increases the risk of respiratory cancer and other damage 4 times higher than smoking the same amount of tobacco (see text). The risk of 0.2 grams of cannabis corresponded to 1 tobacco cigarette. Depending on THC content 0.2 grams of cannabis contain 4 mg (2% THC), 10 mg (5% THC), 20 mg (10% THC) or 40 mg THC (20% THC). About 4 puffs are needed to smoke 0.2 grams of cannabis (see Table 2).



obstructive pulmonary disease (COPD). Epidemiological and experimental data with regard to COPD are conflicting, however. Progressive airways narrowing in COPD can be detected by an accelerated decline in the forced expiratory volume in one second (FEV_1) and by a decreased ratio of FEV_1 to forced vital capacity (FVC). In a study by Bloom et al. (1987), marijuana smokers showed significant lower values for the FEV_1/ FVC ratio than nonsmokers and tobacco smokers. The prevalence of respiratory symptoms was increased. A 6-yr follow-up study with 1802 subjects demonstrated a significant reduction in FEV_1, and FEV_1/FVC in previous marijuana users but not in current users (Sherrill et al. 1991).

In contrast to these findings, a study by Tashkin et al. (1987) comparing marijuana smokers, tobacco smokers, smokers of both tobacco and marijuana, and nonsmokers, did not reveal any association between heavy use of marijuana for more than 15 years and resulting decrements in pulmonary function. None of the values of the applied sensitive measures was different from the average values observed in nonsmokers. In a second study, Tashkin et al. (1997) once more failed to find any association between marijuana use and lung function abnormality. FEV_1 was measured in 131 heavy, habitual smokers of marijuana alone, 112 smokers of marijuana plus tobacco, 65 regular smokers of tobacco alone, and 86 nonsmokers of either substance and in 255 subjects on up to six additional occasions over a period of 8 years. In neither men nor women was marijuana smoking associated with greater declines in FEV_1 than nonsmoking, nor was an additive effect of marijuana and tobacco noted, nor a significant relationship found between the number of marijuana cigarettes smoked per day and the rate of decline in FEV_1. In comparison, tobacco smoking was associated with greater annual rates of decline in lung function than nonsmoking. The authors concluded that "these findings do not support an association between regular marijuana smoking and chronic COPD but do not exclude the possibility of other adverse respiratory effects" (Tashkin et al. 1997, p. 141).

This conclusion is supported by experimental animal studies in which rats were exposed to progressively increasing doses of marijuana or tobacco smoke for six months (Huber et al. 1987, cited according to Tashkin 2001). After sacrifice, the lungs of the tobacco-exposed rats showed morphological and physiological evidence of emphysema, while the rats exposed to marijuana showed no detectable morphologic or physiologic abnormalities compared to unexposed control animals.

However, epidemiological studies suggest that marijuana smoking may increase the risk of respiratory cancer (Tashkin 2001). Bronchial wall biopsies in smokers of marijuana revealed extensive hyperplastic, metaplastic and dysplastic changes believed to be precursors of carcinoma (Fligiel et al. 1997). The damage was similar to that of regular smokers of tobacco, and the effects of marijuana and tobacco appeared to be additive. In a case-control study of

173 patients with newly diagnosed squamous cell carcinoma of the head and neck and 176 cancer-free matched controls, marijuana use was associated with a more than twofold increased risk of head and neck cancer and a dose-response relationship was found (Zhang et al. 1999).

Damage to the mucosa by cannabis smoking, and the presence of pathogens in the plant material may increase the risk of infections, and are of special concern in immunocompromised patients. Cannabis smoke may harbor bacteria and fungi such as *Aspergillus, Mucor* and *Fusarium* species, *Klebsiella pneumoniae, Enterobacter cloacae*, group D *Streptococcus*, some *Bacillus* species and others (for a review see: McPartland 2001).

Performance of the Valsalva maneuver may cause barotrauma to the lung and increase the risk for spontaneous pneumothorax and pneumomediastinum (Feldmann et al. 1993; Miller et al. 1972). Cannabis smokers may typically perform the Valsalva maneuver against a closed glottis after deep inhalation to increase intrathoracic pressure and absorption rate of THC.

HARM REDUCTION WITH INHALATION

The major strategies to reduce the risks of smoking are:

- *The use of cannabis strains with high THC content*. The average concentration of ^{9}-THC in marijuana confiscated in the USA was 4.2% in 1997 (ElSohly et al. 2000). Currently, high-grade cannabis with THC concentrations of 10-20% in the dried flowers is available, reducing the amount necessary for medicinal use and potential damage to the mucosa (see Figure 1). If a strain with a THC content of 10% is used, one puff provides about 5 mg THC (see Table 2). In studies with HIV/AIDS patients, daily doses of 2.5-20 mg have been used to treat anorexia and cachexia, or nausea and vomiting. In a long-term study by Beal et al. (1997) patients received dronabinol orally 2.5 mg once or twice daily to effectively treat anorexia and cachexia in HIV/AIDS. Conant et al. (1991) applied between 2.5 mg dronabinol twice daily and 5 mg three times a day. In a small study by Gorter et al. (1992) participants received between 2×2.5 mg and 4×5 mg dronabinol. Abrams et al. (2000) used smoked cannabis (3.95% THC) and oral dronabinol (3×2.5 mg). Due to the development of some tolerance doses are often increased up to 20 mg with long duration of therapy (personal communications from several physicians), equivalent to one quarter of a marijuana cigarette containing 800 mg of cannabis of 10% THC.
- *The use of pure cannabis*. Sometimes cannabis is smoked together with tobacco or other dried herbs. This procedure should be avoided to minimize the inhalation of smoke from burnt plant material.

- *The use of pipes*. Pipes are superior to cigarettes in some situations in that they easily allow the patient to smoke small amounts of pure high-grade cannabis. The percentage of tars in the smoke is reduced by condensation on the pipe walls. Pipes should be cleaned frequently. Water pipes are inferior to cigarettes and should be avoided (see below).
- *The use of cannabis that is free of natural contaminants and adulterants*. Only disease-free cannabis should be harvested and air-dried. Gross infection with pathogens is easily detectable. Ungerleider et al. (1982) proposed two methods of sterilization: gas-sterilization in a mix of 12% ethylene oxide and 88% dichlorodifluoromethane, and sterilization with Cobalt 60 irradiation. Neither method reduced THC content. Baking plant material in home ovens at 150°C for five minutes kills spores of *Aspergillus fumigatus, A. flavus* and *A. niger* without reducing THC content (McPartland 2001).
- *The use of inhalation devices that reduce output of tars*. Gieringer tested vaporizers that heat marijuana to 180-190°C vaporizing THC below the burning point of cellulose and other plant material. The production of polycyclic hydrocarbons was reduced. The best vaporizer delivered 10 parts of tar to one part of cannabinoids, while in contrast, cannabis cigarettes yielded a ratio of 13:1 (average), and water pipes an average of 27:1 (cited in McPartland 2001). Thus, the best vaporizers achieved a performance ratio about 25% higher than the unfiltered cannabis cigarette, while water pipes were less favorable than cigarettes. The use of a filter in a cannabis cigarette was not advantageous since it not only filtered the tars, but also the cannabinoids. Indeed, the performance ratio was decreased by about 30% compared to the unfiltered cigarette (Gieringer 2000). In a new study Gieringer (2001) was able to demonstrate that combustion products were substantially reduced with another vaporizer. The device used produced THC at a temperature of 185°C while completely eliminating benzene, toluene and naphthalene. Significant amounts of benzene began to appear at temperatures of 200°C, while combustion occurred around 230°C or above. Traces of THC were in evidence as low as 140°C. Carbon monoxide and tars were both qualitatively reduced by the vaporizer, but were not quantified in this study. However, a significant reduction of polycyclic aromatic hydrocarbons was assumed since vaporized cannabis emitted a thin gray vapor and the plant material was left with a green to greenish-brown "toasted" appearance, whereas the combusted sample produced thick smoke and turned to ash.
- *Omission of the Valsalva maneuver and prolonged breathholding*. Several techniques are used to enhance THC absorption in the lungs including the Valsalva maneuver and prolonged breathholding. The first may cause barotrauma to the lung, while the second increases the deposition

of tars (see above). According to two quantitative studies (Tashkin et al. 1991; Azorlosa et al. 1995) that correlated breathholding and resulting effects, longer breathholding enhanced THC effects, thus, confirming in part a common behavior of cannabis smokers. However, extended breathholding did not seem to further maximize absorption. Azorlosa et al. (1995) compared breathholding of 0, 10 and 20 seconds in seven subjects who took 10 puffs of cannabis containing 1.75 or 3.55% THC (Figure 2). Maximum THC plasma concentrations after smoking were 61.2, 146.6, and 130.6 ng/ml with the more potent cigarettes. While THC concentrations significantly increased between the 0 sec and the 10 sec conditions, there was no further increase in plasma concentrations by prolonging breathholding from 10 to 20 sec. Thus, prolonged breathholding may increase the amount of deposited tar without increasing THC absorption.

- *Combination of oral use and inhalation*. In several indications, a combined regime of a basic oral medication with cannabis or THC and a demand inhaled medication may be useful to reduce risks from smoking and overdosage with oral administration. Similar regimes are routine with opiates to treat chronic and breakthrough pain (Stevens and Ghazi 2000).

RISKS OF ORAL USAGE

Responsiveness to the action of THC shows a high inter-individual variation. 10 mg of oral THC will not consistently result in psychic alterations, but in some persons even 2.5 mg produce recognizable effects. In a study by Chesher et al. (1990) of a healthy population dosed orally with 5 mg THC, no difference was found to placebo controls as to the subjective level of intoxication. Doses of 10 and 15 mg THC caused slight differences compared to the placebo, and a dose of 20 mg, finally, caused marked differences in subjective perception. In a clinical study by Beal et al. (1995) in AIDS patients some patients experienced mostly mild to moderate side effects (euphoria, dizziness) with 2.5 mg dronabinol twice daily. Lucas and Laszlo (1980) found pronounced psychotropic reactions (anxiety, marked visual distortions) in patients undergoing cancer chemotherapy that had received 15 mg THC/m^2 (square meter of body surface), which corresponds to about 25 mg THC in an average adult person of 1.7 m^2 body surface area. A reduction to 5 mg THC/m^2, about 7.5-10 mg THC, produced only mild reactions. In a study by Frytak et al. (1979) in cancer patients receiving 15 mg dronabinol three times a day as an antiemetic, 52% reported a "high." Brenneisen et al. (1996) administered single oral doses of 10 or 15 mg THC to two patients. Physiologic parameters (heart rate) and psychological parameters (concentration, mood) were not modified by the administration.

TABLE 2. Dosing-scheme for cannabis taken orally and smoked

Amount of cannabis taken	THC content in herbal cannabis		
	2% THC	5% THC	10% THC
oral			
0.05 g	1 mg THC	2.5 mg THC	5 mg THC
0.1 g	2 mg THC	5 mg THC	10 mg THC
0.2 g	4 mg THC	10 mg THC	20 mg THC
0.5 g	10 mg THC	25 mg THC	50 mg THC
smoking*			
1 puff (0.05 g)	1 mg THC	2.5 mg THC	5 mg THC
2 puffs (0.10 g)	2 mg THC	5 mg THC	10 mg THC
4 puffs (0.20 g)	4 mg THC	10 mg THC	20 mg THC
8 puffs (0.40 g)	8 mg THC	20 mg THC	40 mg THC
16 puffs (0.80 g)	16 mg THC	40 mg THC	80 mg THC

* Ingested THC was calculated according to the formula: x = amount of cannabis/100 by THC content. It was assumed that an average of 50 mg of cannabis are smoked with one puff, calculated from the following data. Marijuana cigarettes provided by the U.S. National Institute of Drug Abuse (NIDA) weigh about 800 mg (Azorlosa et al. 1992, Azorlosa et al. 1995). Perez-Reyes et al. (1981) noticed that about 24 puffs were necessary to smoke a low-dose NIDA marijuana cigarette, corresponding to 33 mg of cannabis per puff. Liguori et al. (1998) used a smoking regime with 64 mg marijuana per puff. It should be noted that THC becomes concentrated in the uncombusted parts of a cigarette so that the first puffs yield a little less THC than the later (Tashkin et al. 1991).

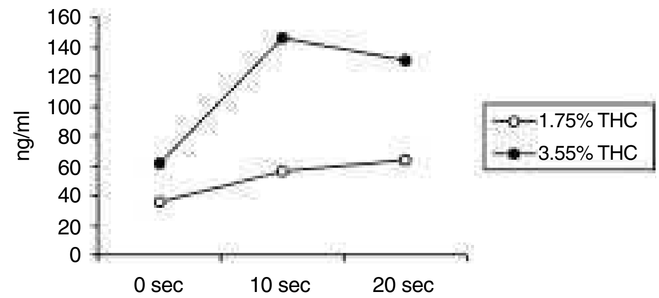
Additionally, there may be an intra-individual variance of THC absorption, especially if the drug is taken under different conditions. Intestinal absorption and degradation of THC may depend on several factors. As with opioids, onset of action might depend on the presence or absence of food. Immediate release oral opioid preparations are known to require about 30 minutes to onset of analgesic action taken on an empty stomach, but onset of action may be delayed when taken on a full stomach (Stevens and Ghazi 2000).

Due to the delayed onset of action, oral cannabis products may be difficult to dose precisely, resulting in either overdosage or underdosage, an observation often reported by physicians of the nineteenth century (Fankhauser 2001).

HARM REDUCTION WITH ORAL USE

The major risk associated with oral cannabis use is overdosing. To achieve appropriate dosing two principles should be followed:

FIGURE 2. Average plasma THC levels (ng/ml) in seven healthy young males following ten puffs from a cannabis cigarette containing 1.75 or 3.55% THC with a breathholding duration of 0, 10, and 20 seconds immediately after smoking (drawn according to data from Azorlosa et al. 1995).



- Ascertainment of optimal individual dose by slowly increasing doses.
- Intake of the medication under the consistent conditions, especially with regard to vehicle and filling of the stomach.
- Subsequent administration of supplemental doses by inhalation.

If possible, slowly increasing doses should be applied in a titrated fashion to avoid undesirable side effects on psyche and circulation. Starting doses are 2×2.5 mg or 2×5.0 mg of dronabinol per day. Dosages may be increased up to several units of 10 mg daily. In AIDS wasting and HIV related nausea and vomiting 5-20 mg THC daily are usually sufficient (Beal et al. 1995; Beal et al. 1997; Gorter et al. 1992; Abrams et al. 2000). If natural cannabis products of unknown THC content are used orally, the patient should begin with about 0.05-0.1 g of the drug (for cannabis with an average THC content of 5% this corresponds to 2.5-5 mg THC, see Table 2).

If possible, the THC content should be determined in a laboratory. If this is not possible, a store of cannabis sufficient for several weeks should be secured so that a constant quality is ensured. In a study by Fairbairn et al. (1976) the THC content of marijuana only decreased by 7% within 47 weeks with dry storage in the dark at 5°C, and by 13% at a temperature of 20°C.

To achieve reproducible effects, cannabis or THC should always be ingested under similar conditions with regard to food intake, e.g., one hour before a meal. If natural cannabis preparations are used, doses should be weighed carefully and taken with the same carrier, e.g., tea with half a gram of dried cannabis flowers in half a liter of water and some cream.

As with opiates, some side effects may decrease within a period of days or weeks, thereby increasing the acceptance of the drug. Prolonged THC inges-

tion causes tolerance to orthostatic hypotension, tachycardia and psychological effects (Benowitz and Jones, 1975), so that daily doses of more than 50 mg THC may sometimes be taken without significant undesirable psychic or physical side effects (Holdcroft et al. 1997). Heavy chronic users in western societies may smoke five to ten cannabis cigarettes per day, thus well tolerating daily doses of 100 mg THC and more. In a sample analyzed by Solowij (1991) mean weekly consumption was 766 mg of THC, with a range from 30-2400 mg THC.

Tolerance may also arise with respect to therapeutically desired effects (e.g., decrease of intraocular pressure, analgesia), and require increased doses (Jones et al. 1981). O'Shaughnessy (1839) reported development of tolerance in connection with the medical use of a cannabis tincture in rheumatism: Two of three treated patients showed good improvement, while the third patient did not respond to the drug. He finally admitted to being a habitual user.

Duration of tolerance to THC differs depending on effect. In mice hypothermia, depression of intestinal motility and spontaneous locomotor activity were investigated (Anderson et al. 1975). Normal hypothermic responses returned after 12 dose-free days and baseline locomotor activity returned within 4 days. Tolerance to the depressant effect on intestinal motility still persisted after 19 dose-free days. According to self-reports of patients to the author, tolerance may remain for some weeks to months after stopping the drug.

TREATMENT OF ACCIDENTAL OVERDOSE

Ingestion of cannabis and THC may result in unwanted effects on the circulatory system (increased heart rate, changes of blood pressure) and psychological effects such as an acute panic reaction and hallucinatory experiences (Hall and Solowij, 1998).

Tachycardia may be undesirable in persons suffering from coronary heart disease. It seems to be caused by sympathetic stimulation and can be treated by beta-blockers. Perez-Reyes et al. (1973) used propranolol infused at a rate of 0.5 mg per minute for 6 minutes to block the acceleration of heart rate following oral administration of 35 mg THC in different vehicles. The psychological effect was not altered. Thus, it may be also possible to use beta-blockers as prophylactic agents in individuals with heart disease without influencing other specific effects of THC, including therapeutic actions. In case of orthostatic hypotension or syncope, the patient should lie down with the legs elevated.

"Talking the patient down" may treat dysphoric states. If this proves insufficient, intravenous diazepam (5-10 mg) may be administered (Perez-Reyes et al. 1973).

ALTERNATIVE FORMS OF DELIVERY

Many other forms of application have been tested experimentally, decreasing the time until onset of action compared to oral use and leading to more reliable reproduction of effects. Some routes may be promising in the future.

Sublingual: At the 2000 Meeting of the International Cannabinoid Research Society a British group presented data on studies performed with three different sublingual cannabis extracts (Guy et al. 2000). They had been administered to six healthy volunteers receiving up to 20 mg THC. The group reported that sublingual administration of cannabis extract resulted in relatively fast effects and was well tolerated. No quantitative data on bioavailability are yet available.

Rectal: A few studies have been conducted with rectal THC preparations (Mattes et al. 1994; Brenneisen et al. 1996). Bioavailability strongly differed depending on suppository formulations. Among the formulations containing several polar esters of ^{9}-THC in various suppository bases, ^{9}-THC-hemisuccinate in Witepsol H15 showed the highest bioavailability (ElSohly et al. 1991), about as twice as high as with oral administration in man (Brenneisen et al. 1996).

The author of this article is aware of experiments by several cannabis users, who rectally self-administered natural cannabis preparations. In one example, dried milled cannabis flowers were cooked in cocoa butter for one hour. After cooling, suppositories were formed. The effect was noticeable within about ten minutes. No scientific data are available in this regard. These personal experiences contrast with experimental data according to which unchanged delta-9-THC is not bioavailable by the rectal route (Perlin et al. 1985; ElSohly et al. 1991).

In a study by ElSohly et al. (1991) with various esters of THC in both lipophilic and hydrophilic suppository bases (Witepsol H15 and polyethylene glycol), no delta 9-THC or its metabolites were detected in the blood samples using the Witepsol H15 with the exception of the hemisuccinate ester. Using polyethylene glycol, only low levels of delta 9-THC and its metabolites were detected in blood for all esters tested.

Transdermal: The scientific literature provides little specific information on the transdermal uptake of THC from topically applied preparations. There are only two experimental studies investigating the skin permeation behavior of THC (Touitou and Fabin 1988; Touitou et al. 1988). These investigations were designed to develop an effective transdermal delivery system for THC, an antiemetic in patients receiving cancer chemotherapy. Researchers in this study used ^{8}-THC since this molecule is more stable than the ^{9}-THC.

Generally, the human skin is well protected against penetration by external substances. Many topically applied substances attain a systemic bioavailability of only a few percent (Hadgraft 1996). The main barrier to penetration

is the cornified layer of the stratum corneum. There is evidence that only a small fraction of strongly lipophilic substances, such as THC, overcome the hydrophilic phases of the intercellular space between the cells of the stratum corneum (Bast 1997).

However, the uptake of compounds via the skin can be influenced by the presence of other compounds in the matrix. Penetration enhancers may disrupt the stratum corneum lipids, interact with intercellular proteins, or improve the partitioning of a compound. These may include synthetic chemicals such as dimethylsulfoxide (DMSO), surfactants, and certain unsaturated fatty acids, e.g., oleic acid.

The research by Touitou et al. (1988) showed that the permeability coefficient of ^{8}-THC was significantly enhanced by water and by oleic acid in propylene glycol and ethanol (PG-EtOH). Significant THC concentrations in the blood of rats treated with formulations containing 26.5 mg/g THC on the skin were measured. The permeability coefficient of THC was increased 6 times by 3% oleic acid in PG-EtOH solutions and 14 times by 3% oleic acid in PG-EtOH-H_2O solutions (Touitou and Fabin 1988).

An Albany College of Pharmacy research team was awarded a $361,000 three-year grant in January 2000 by the American Cancer Society to study whether cannabinoids can be absorbed effectively through the skin (Gormeley 2000). The research is intended to develop a cannabinoid patch for therapeutic use and is expected to require several years for completion.

The US Patent and Trademark Office granted a patent for a "Cannabinoid patch and method for cannabis transdermal delivery" on September 5, 2000 (United States Patent 6,113,940). The patent describes a trial in two subjects who received 0.2 g of cannabis oil in a carrier (DMSO). The patch was applied to the underside of the wrist of two human subjects. According to the patents, subjective THC effects were noted within ten minutes and lasted four to six hours.

SOME COMPARISONS TO OPIUM OPIATES

There are some parallels between opiates and cannabinoids with regard to mechanism of action and indications (Vaughan and Christie 2001), which shall be discussed in brief, mainly with regard to side effects and routes of administration.

Cannabis (*Cannabis sativa* L.) and opium (*Papaver somniferum* L.) are used recreationally, most often by inhaling the smoke of the burnt plant material. In contrast to cannabis, the illegal use of single opium compounds (natural opiates and their derivatives) are more common today than the use of whole plant preparations. As with cannabis, the specific chronic health effects associ-

ated with the use of illegal opiates and opioids largely depend on the route of application.

While smoking is the major route of application for cannabis, it is injection into the blood vessels for opiates. Injection may result in local injury and inflammation, and in the transmission of hepatitis C and HIV through contaminated needles. The chronic use of non-injected opiates seems to cause only minor health effects (Hall et al. 1999). It is remarkable to note that smoking is generally regarded as a minor health hazard in context with opiates (Hall et al. 1999) but seems to be of greater concern in context with cannabis (Joy et al. 1999).

Opium contains about 25 alkaloids. As with cannabis there is one most prominent ingredient. Morphine is present in the plant with 10-15% of dry plant weight. However, there are other pharmacologically potent alkaloids in relevant concentrations, particularly codeine (1%-3%), noscapine (4%-8%), and papaverine (1%-3%).

In addition to the medical use of single natural constituents of opium (morphine, codeine, noscapine), doctors in many countries (e.g., Germany) may also prescribe whole opium preparations. The effects of opium differ qualitatively from that of morphine. Due to the presence of other alkaloids, especially papaverine, opium causes an atonic constipation, in contrast to a spastic constipation with morphine (Mutschler 1996). The difference between whole cannabis and single dronabinol remains to be elucidated, and it is unclear whether this difference is less prominent than between opium and morphine (see McPartland and Russo 2001 in this issue).

There are major differences between the pharmacokinetics of opiates and cannabinoids. To achieve a fast onset of action, hydrophilic opiates may be given intravenously. But the intravenous application of THC is complicated by its lipophilic properties. Even oral opiates have a faster onset than oral cannabinoids (30 min versus 30-90 min) and show a more constant and reliable absorption (Cleary 1997). In contrast to the situation with opiates, there is currently no good available alternative to the inhalation of cannabis or cannabinoids if a fast onset of action is required. The sublingual application of cannabis preparations currently under investigation in clinical studies in the United Kingdom seems to be a promising route.

PRINCIPLES OF HARM REDUCTION WITH CANNABIS

Natural cannabis is usually inhaled. However, this route of administration is often used even if the advantages over oral application are not really of relevance to achieve optimal therapeutic benefits. In cases where inhalation is the best way to administer cannabis or single cannabinoids, techniques designed

to reduce risks to the mucosa should be applied. Harm reduction with regard to the medical use of cannabis may include the following strategies:

- Relinquishment of inhalation and replacement by other routes of administration if possible, or combination of several routes.
- Minimization of damage to the respiratory tract with appropriate techniques including the use of cannabis with high THC content, inhalation with vaporizers, avoidance of the Valsalva maneuver and prolonged breath holding over 10 sec.
- Avoidance of accidental over-dosing through thorough dosing procedures with oral ingestion.
- Development and improvement of non-smoked, parenteral application forms, including the rectal, sublingual, and transdermal route.

Taken together these maxims allow reduction in the risks associated with the oral and inhalation routes of administration to a tolerable degree.

Since many physicians reject the concept of smoking medication on principle, it may be helpful to look at this controversial topic in a broader context. To ingest 20 mg of THC, 0.2 g of cannabis (or a quarter of a cigarette) with a THC content of 10% has to be smoked (see Figure 1). Even if a 4-fold health risk potential for cannabis smoke compared to tobacco smoke is assumed, this would result in an equivalent of the respiratory risks associated with smoking one tobacco cigarette a day.

The principle *nihil nocere* ("do no harm"), and the association with recreational usage of cannabis may be regarded as the two major reasons for dismissing smoking. This rejection may evoke a more emotional than scientific attitude towards this question. It should be noted that other accepted routes of administration for many drugs designed to achieve a rapid onset of action are associated with multiple risks, even fatal ones, and various drugs also damage the mucosa. Intravenous or intramuscular application of a drug may harm surrounding tissues and in some cases may produce severe damage. Oral administration of various drugs adversely affects the mucosa of the intestinal tract, among them widely used non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and acetylsalicylic acid. We customarily accept relatively high medical risks, as with intrathecal administration of opioids, if the anticipated benefits outweigh those drawbacks. The inhalation of a limited amount of combustion products with smoked cannabis may be regarded as a rather low and acceptable risk as well, if the benefit for a patient is high.

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Cannabis "Vaporization": A Promising Strategy for Smoke Harm Reduction

Dale H. Gieringer

SUMMARY. The primary health hazard of medical cannabis is respiratory damage from marijuana smoke. Aside from oral ingestion and other non-smoked delivery systems not yet commercially available, strategies for reducing the harm of smoking include: (1) use of higher potency cannabis and (2) smoking devices aimed at eliminating toxins from the smoke. Studies have found that waterpipes and solid filters are ineffectual at improving the THC/tar ratio in cannabis smoke. The most promising alternative appears to be "vaporization," in which cannabis is heated to a point where cannabinoids are emitted without combustion. A feasibility study by NORML and MAPS has demonstrated that an electric vaporizer can successfully generate THC at 185°C while completely suppressing benzene, toluene, and naphthalene formation. Further studies are needed to evaluate how effectively vaporizers suppress other toxins, and how their performance varies using different samples, temperatures, and device designs.

Dale H. Gieringer, PhD, Coordinator, California NORML (National Organization for the Reform of Marijuana Laws) (E-mail: www.canorml.org; canorml@igc.org).

Address correspondence to: Dale H. Gieringer, PhD, 3514 Dwight Way, Berkeley, CA 94704.

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INTRODUCTION

A leading health concern about the medical use of cannabis is respiratory sequelae due to smoking. Aside from its active cannabinoids, marijuana smoke greatly resembles tobacco smoke, containing noxious tars and gases that are a byproduct of leaf combustion. These include highly carcinogenic polycyclic aromatic hydrocarbons (PAHs) and other known carcinogens, such as benzene, at levels comparable to those in tobacco smoke. Also included are numerous other toxic inhalants, among them carbon monoxide, toluene, naphthalene, acetaldehyde, phenol, and hydrogen cyanide, again at levels comparable to tobacco (Huber 1991; Institute of Medicine 1982).

There is accordingly good reason to believe that chronic marijuana smoking poses many of the same respiratory hazards as tobacco. These hazards are offset by the fact that marijuana users typically consume a fraction as much material as tobacco smokers (1 g per day for a typical daily user, or 4 g per day for a very heavy, one-ounce per week medical patient, versus 20 g per day for a pack-a-day cigarette smoker). On the other hand, marijuana has been shown to deliver four times as much tar to the lungs per weight smoked as tobacco, possibly due to the deep breath holding of marijuana smokers (Wu et al. 1988).

On balance, the evidence indicates that marijuana smoking is not as great a public health hazard as tobacco. Epidemiological studies have yet to find evidence of lung cancer or increased mortality in frequent cannabis users (Sidney 1997a, 1997b). Unlike tobacco, cannabis lacks nicotine, a major risk factor in heart disease. Long-term studies of heavy users by Tashkin have found no evidence of a link between marijuana smoking and emphysema (Tashkin 1997, Zimmer and Morgan 1997).

Nonetheless, there is solid evidence to show a link between heavy cannabis smoking and respiratory disease. A succession of clinical studies have found that long-term, frequent marijuana smokers exhibit signs of respiratory damage, including chronic bronchitis, sore throat, inflammation, impaired immune function, and pre-cancerous cell changes (Tashkin 1993). A survey of patients at the Kaiser Permanente medical centers found that marijuana smokers suffered a significantly higher incidence of respiratory complaints (Polen et al. 1993). There have also been anecdotal reports of neck and throat cancers in heavy marijuana smokers, most of whom also smoked tobacco. Another concern in light of the widespread use of cannabis among AIDS patients is that heavy marijuana smoking might increase susceptibility to lung infections such as *Pneumocystis carinii* pneumonia, although such a risk has not been proven.

In sum, respiratory harm has been rightly called "the only well-confirmed deleterious physical effect of marijuana" in the words of Dr. Lester Grinspoon (Grinspoon 1997, p. 250). Given the growing public pressure against smoking tobacco, these concerns have loomed large as an obstacle to acceptance of medical marijuana by public health authorities. In its review of medical marijuana, the Institute of Medicine of the National Academy of Sciences found "no future" in smoked marijuana, saying, "Because marijuana is a crude delivery system that also delivers harmful substances, smoked marijuana should generally not be recommended for medical use" (Institute of Medicine 1999, pp. 10-11). However, the IOM failed to consider various harm reduction techniques that might substantially reduce the hazards associated with smoking cannabis.

In this study, we will discuss the state of the art of marijuana smoke harm reduction, focusing particularly on smoking devices such as waterpipes and vaporizers aimed at reducing the toxins in cannabis smoke. Before doing so, however, it is worth briefly discussing other strategies for respiratory harm reduction.

SMOKE HARM REDUCTION STRATEGIES

The most obvious alternative to marijuana smoking is to ingest cannabis orally via tinctures, extracts, foodstuffs, or capsules. The limitations of oral dosages are well known and substantial (Grinspoon 1997). Oral THC is notoriously unreliable in its effects. The bioavailability of oral cannabinoids varies greatly depending on the individual patient and the state of his or her metabolism and digestive system. Unlike inhaled cannabis, the effects of which become readily apparent within seconds, allowing the patient to regulate the dose via self-titration, oral dosages require up to an hour or more to take effect. Over- or under-dosage is therefore a common problem. The delayed onset of oral cannabis also renders it unsuitable for conditions requiring prompt treatment, such as acute pain or convulsions. In addition, oral dosages are hard to keep down for patients suffering intense nausea. Finally, oral dosages do not have the same pharmacological action as inhaled marijuana, since orally ingested THC does not pass directly into the bloodstream, as with smoking, but is rather processed by the liver, where it is transformed into another, even more psychoactive metabolite, 11-hydroxy-THC (Zimmer and Morgan 1997). The medical implications of this are unknown, though they might include an increased risk of adverse "panic reactions." Historically, the declining interest in medical cannabis at the turn of the last century was attributed to the unreliability of its effects, which may be explained by its oral dosage form. The manifold drawbacks of oral preparations such as synthetic oral THC (dronabinol,

Marinol) have led most of today's patients to prefer inhaled marijuana; however, a survey of medical cannabis patients found only minor differences in the subjective effects of oral and smoked herbal cannabis (Corral 2001).

Other non-smoked routes of administration have been proposed, but have not reached the stage of commercial fruition. Topical applications such as cannabis leaf poultices have been used in folk medicine, but their efficacy is dubious and unproven. A patent for a transdermal cannabinoid patch was recently filed by a California company, General Hydroponics (US Patent 6,113,940; http://www.farmacy.org/patch.html), but its efficacy has yet to be demonstrated in FDA trials. While THC is not suited for transdermal application because of its high lipophilicity (Institute of Medicine 1999), the possibility remains that other pharmacologically active cannabis derivatives can be transported through the skin.

Cannabinoid eye drops have been proposed to treat glaucoma, but have yet to be successfully tested in the USA (Grinspoon 1997; Green et al. 1976).

A rectal cannabinoid delivery system has been demonstrated by ElSohly using suppositories that deliver a pro-drug that transforms into THC. This could be a practical alternative to oral dronabinol for patients with extreme nausea. This system is currently under licensed development by Oxford Natural Products in the U.K. (ElSohly 2000).

The most appealing alternative to smoked marijuana would seem to be some form of cannabinoid inhaler. Attempts to aerosolize THC have encountered technical difficulties in the past (Tashkin 1977). However, Pertwee has recently announced the development of a cannabis spray based on a new, water-soluble cannabis-compound developed in collaboration with Razdan and Martin. Approval by the U.K. is expected within five or ten years (BBC News 2000). Meanwhile, four new delivery systems for synthetic THC (dronabinol, Marinol) are being investigated in Phase I studies by Unimed: deep lung aerosol, nasal spray, nasal gel and sublingual preparations (Institute of Medicine 1999). Similar delivery systems for natural cannabis extracts are under investigation by GW Pharmaceuticals in the U.K. (Hadorn 2001). New delivery systems are likely to be approved for marketing in the next few years, at least in certain countries. However, their usage and availability will be limited by licensing and regulatory restrictions to certain approved products. For the foreseeable future, many users will therefore continue to find them unobtainable or unaffordable.

For the immediate future, smoked marijuana is therefore likely to remain the most popular and accessible form of cannabis, both medicinally and otherwise. The question thus arises as to how to reduce its harmfulness to the respiratory system.

One obvious answer is to use higher-potency sinsemilla (Spanish for "without seed"), or hash oil extracts so as to boost the proportion of THC in the

smoke, thereby necessitating a smaller intake of smoke. Obviously, this assumes that patients can reliably adjust their smoke intake to deliver a given desired dose of cannabinoids. It also assumes that the smoke from higher-potency preparations delivers proportionately higher ratios of cannabinoids to toxins–an assumption that may not hold if their chemical consistency and combustion properties are substantially different from that of regular cannabis.

SMOKING DEVICES

Another promising strategy for smoke harm reduction is to separate or eliminate the harmful toxins from the useful cannabinoids via some sort of purification or filtration device. A profusion of smoking devices are currently available on the underground market and are in use by medical marijuana patients. Although most have no evident health benefits, a few purport to offer harm reduction attributes.

Assuming that patients aim to achieve a given dose of cannabinoids, the proper measure for smoke harm reduction should be the overall ratio of cannabinoids to toxins. The higher this ratio, the fewer the noxious smoke byproducts patients have to take into their lungs in order to achieve a given effective dose.

Three basic kinds of smoking devices are presently in use for marijuana smoke harm reduction:

- *Waterpipes:* Marijuana smoke can be inhaled through waterpipes, bongs or similar devices in the hopes of cleansing the smoke via water filtration. Many patients strongly prefer to smoke cannabis through waterpipes, feeling that they deliver smoother, cooler, less irritating smoke. Studies indicate that water filtration can be effective in reducing tars and other toxins in tobacco and marijuana smoke (Cozzi 1993). The problem is that such devices may also filter out medically active cannabinoids, degrading the actual cannabinoid/toxin ratio (Gieringer 1996).
- *Solid filters:* Smoke can also be inhaled through solid filters such as those in tobacco cigarettes. Cigarette filters are known to produce modest reductions in tobacco smoke tars, and can also be used with cannabis. Once again, the problem is that they also filter out active THC (Gieringer 1996). The essential question therefore remains as to whether solid filters can actually improve the cannabinoid/toxin ratio.
- *Vaporizers:* Observations by users and laboratory studies described below indicate that it is possible to generate psychoactive vapors from cannabis by heating it to a temperature below the point of combustion, where the bulk of carcinogens are formed. This process is popularly re-

> ferred to as "vaporization" or "volatilization." (In actuality, the exact physical process is uncertain: the Merck Index lists the vaporization point of THC as 200°C *in vacuo*, but users have reported psychoactive vapors at temperatures ≤180°C under normal atmospheric pressure.) In theory, an ideal vaporizer would deliver a stream of medically active cannabinoids without any of the toxic byproducts of combustion. In practice, experimental vaporizers are observed to produce a light stream of apparently cannabinoid-laced vapors, without heavy smoke or ash, leaving the marijuana crisped with a toasted, green-to greenish-brown appearance. Although numerous models of vaporizers are currently available on the market, none have been subjected to FDA-style efficacy testing, and they remain technically illegal for medical cannabis use under current paraphernalia laws.

Until recently, there has been little scientific basis on which to judge the alternative marijuana smoking harm reduction strategies. However, a handful of recent studies have begun to shed light on the subject.

NORML/MAPS SMOKING DEVICE STUDY

In an effort to evaluate the feasibility of marijuana smoking harm reduction, California NORML (National Organization for the Reform of Marijuana Laws) and MAPS (Multidisciplinary Association for Psychedelic Studies) sponsored a study of seven different smoking devices: three different waterpipes, two electric vaporizers, a joint fitted with a cigarette filter, plus a regular unfiltered joint as a control (Gieringer 1996). The study was designed to assess the ratio of cannabinoids to tar for each device, on the theory that higher THC/tar ratios would correlate with reduced respiratory hazards.

Samples of government-supplied marijuana from the National Institute on Drug Abuse (NIDA) were puffed in a smoking machine in a manner designed to mimic human marijuana smoking. The smoke was collected in Cambridge glass fiber filters designed to capture particles > 0.1 microns, which are used to separate solid particulates or "tars" from gaseous smoke components such as carbon monoxide. The filtered solids also include all of the cannabinoids. The filtered residue was weighed to measure total tar content and quantitatively analyzed for three cannabinoids, THC, CBD and CBN, by means of a gas chromatograph/mass spectrometer (GC/MS).

As expected, all of the devices produced a reduction in tars relative to the control: 33% for the filter, 89%-98% for the waterpipes, and 56%-97% for the vaporizers (Table 1). However, only the vaporizers achieved an improvement in the ratio of tars to cannabinoids. The cigarette filter performed worse than

TABLE 1. Tar and Cannabinoid Delivery–7 Smoking Devices

	Nonfilter Cigarette	Filter Cigarette	Waterpipe #1	Waterpipe #2	Waterpipe #3	Vaporizer #1	Vaporizer #2
Total Tars (mg/puff)	309.8	140.5	24.5	9.2	78.3	4.76	11.3
Total Cannabinoids (% Tar)	7.82	5.32	5.46	4.48	2.50	7.89	9.82
Total THC (%Tar)	5.99	4.12	4.31	2.14	3.36	6.27	5.24

Adapted from Gieringer, D. "Marijuana Waterpipe and Vaporizer Study," 1996

the unfiltered joint, producing 30% more tar per cannabinoids. Worse yet were the waterpipes, which produced from 30% to 180% more tars per cannabinoids. Ironically, the worst waterpipes were those designed to maximize the vapor's exposure to water. The disappointing implication is that waterpipes may actually be counterproductive in reducing tars from cannabis smoking.

A likely explanation for the poor performance of physical filtration systems is that THC molecules are especially sticky and apt to adhere to other smoke particles. Any attempt to screen out the latter is therefore apt to pick up the former as well. Indeed, to the extent that cannabinoids are relatively stickier than other compounds, particles containing them may be more likely to be trapped by filters.

The vaporizers were the only devices to outperform the unfiltered joint, though only by a modest margin. The first vaporizer, a commercial model consisting of a battery-powered metal hot plate inside a jar to trap the vapor, achieved a 26% improvement in the cannabinoid/tar ratio. The second model, a homemade, hybrid device, consisting of a hot air gun blowing through a beaker of water, combined vaporization with water filtration. It achieved a statistically insignificant 0.25% improvement. However, its performance may well have been degraded by the water filtration component, the inclusion of which seemed in retrospect to be a design flaw in the experiment.

Evaluation of the vaporizers was further complicated by the fact that the "hot plate" model produced anomalously high amounts of CBN and 30% less THC. The origins of the CBN are not certain, but might well be due to partial pyrolysis of THC (Fehr and Kalant 1972). Since CBN has negligible pharmacological activity compared to THC, it seemed appropriate to recompute the device performances in terms of the ratio of THC to tars. When this was done, the hotplate turned out to be 13% worse than the unfiltered joint, while the hot air device was 4.6% better.

The most disappointing finding of the smoking device study was the apparent counter-productivity of waterpipes and cigarette filters. However, this con-

clusion must be qualified by several important caveats due to limitations in the study design:

- The gaseous component of the smoke was not analyzed in the study. Cannabis smoke contains numerous noxious gases, including hydrogen cyanide, which incapacitates the lung's defensive cilia, volatile phenols, which contribute to the harshness of the taste, aldehydes, which promote cancer, and carbon monoxide, a known risk factor in heart disease (Huber 1991). There is evidence that water filtration may be quite effective in absorbing some of these gases, especially those that are water-soluble (Cozzi 1993). If so, waterpipes could still turn out to have some health benefits.
- The study did not attempt to quantify the specific chemical components of the tars except for the cannabinoids. It is conceivable that the tars from the waterpipe or cigarette filter contained relatively less harmful toxins and carcinogens, and more inert ingredients, than the unfiltered ones.
- In conformity with cigarette smoking conventions, a 30-cm butt length was left unsmoked on the unfiltered joint. Thus, the study did not test the last part of the joint, the "roach," which is commonly savored to complete exhaustion by marijuana connoisseurs. The roach is known to accumulate higher concentrations of tars and THC from the rest of the cigarette (Tashkin et al. 1991a). It is possible that the cannabinoid/tar ratio for the unfiltered joint would have been considerably different if the roach had been included. It is also possible that there are other ways in which the smoking machine did not accurately replicate the inhalation pattern of human smokers.

Although the vaporizers showed at best marginal effectiveness in the study, substantial improvements might have been realized with more careful research and development. Neither vaporizer was carefully designed, adjusted, or optimized for laboratory testing. Furthermore, unlike waterpipes and filtration devices, vaporizers are at least based on a physical principle that offers a theoretical hope for further development. For this reason, NORML and MAPS decided to undertake a second study devoted specifically to vaporizers, preliminary results of which are presented below.

SOUTH AUSTRALIAN GOVERNMENT STUDY

A study sponsored by the South Australian Drug and Alcohol Services Council confirmed the apparent inefficacy of waterpipes, while raising confusing new issues about marijuana smoke harm reduction (Gowing et al. 2000).

The study tested 12 different varieties of cannabis, ranging from low-grade leaf to high-potency sinsemilla. All samples were dried, trimmed, shredded and homogenized in a blender. The samples were smoked in standard joints, in waterpipes, and in combination with tobacco using a Filtrona smoking machine under standard cigarette smoking conditions. Particulate matter was trapped in Cambridge type glass fiber filters. The smoke was analyzed for THC yield, tar, water, and carbon monoxide.

The study found that the waterpipes consistently generated more tars and carbon monoxide than the unfiltered cigarettes. Tar yields were on the order of 3 to 7 times higher per given sample, while carbon monoxide was 2 to 4 times higher. Unfortunately, no comparative data on THC yield were produced, making it impossible to assess the overall THC/tar and CO ratios. Nonetheless, the researchers concluded that the risks of cannabis smoking were less likely to be reduced by a waterpipe as opposed to a cigarette.

A significant part of the difference between waterpipes and cigarettes could be explained by differences in smoking conditions. Whereas the cigarettes had been puffed at 60-second intervals, the waterpipes had to be puffed at 6-second intervals in order to keep them lit. When the cigarettes were re-tested at 6-second intervals, it was found that two-thirds of the increase in tar content and one-third of the increase in CO were accounted for. (Again, there were no THC data to assess what change may have occurred in the relative THC/tar and CO ratios.) Another factor that could have explained the higher tar from the waterpipe was that the cigarettes were smoked to a butt length of 23 mm, while the waterpipe smoke was drawn directly into the smoking machine. Hence, the butt may have filtered out more tars and CO from the cigarette smoke.

A startling finding of the study was that the composition of the smoke varied widely depending on the specific samples and smoking conditions. In particular, THC yields varied radically for different samples and devices. In the case of cigarettes, no clear correlation was observed between the potency of cannabis smoked and the amount of THC actually delivered in the smoke. One cigarette of 0.69% THC leaf delivered smoke of 0.62% THC content, while another cigarette of 12.97% flowering "heads" yielded only 0.54% THC in smoke, a remarkable 25-fold difference in efficiency of THC delivery. In the case of waterpipes, smoke and sample potency were better correlated, although not in full proportion. For example, high-grade samples of 9-13% potency yielded no more than 2.4% THC in waterpipe smoke, while low-grade samples of 2% yielded amounts ranging from 0.08% to 1.1%. These results are strikingly at variance with the observations of many experienced users, who report that one or two tokes (inhalations) of good, high-grade sinsemilla can be equivalent to a whole cigarette of regular cannabis. Such discrepancies may be explained by peculiarities in the particular samples tested or by systematic differences between human smoking and the laboratory smoking machine used in

the Australian study. In any event, the Australian study implies that higher cannabis potency does not necessarily translate to more available THC.

The investigators inferred that actual THC delivery is highly dependent on the particular sample and smoking conditions, including puff length, temperature, and other factors. In particular, tests showed a significant, positive correlation between THC delivery and water content of the smoke for both cigarettes and waterpipes. It is unknown how the water content of the smoke was related to the original water content of the samples as opposed to other factors, such as temperature of combustion. For example, it is possible that excessively moist samples could have produced *less* water and THC in the smoke if they burned less efficiently. The most that can be concluded is that THC yield is related to factors that are also related to water yield. It has been proposed that THC is normally released not via pyrolysis or volatilization, but by a process of co-distillation with steam, in which cannabinoids are expelled along with water vapor in the 2 mm high temperature gradient zone before the burning front (Fehr and Kalant 1972). This hypothesis seems bolstered by the finding that THC and water yield are correlated.

Further evidence for the importance of smoking conditions with respect to THC yield was seen when tobacco was added to the cannabis. When mixed with 50% tobacco and 50% cannabis, the cigarettes yielded between 93% less and 81% *more* THC. The waterpipes performed more consistently with expectations, yielding 30-55% less THC in most cases. Tar levels increased when tobacco was added to cigarettes but generally held steady for waterpipes, while carbon monoxide increased for both, though more so in waterpipes. The samples that had the worst THC delivery in cigarettes showed the most marked improvement when combined with tobacco. This suggested that the tobacco had made the samples burn better, perhaps by raising the temperature so as to release more THC.

VAPORIZER STUDIES

The theory supporting vaporization has been known for sometime. A vaporizer known as the Tilt was commercially marketed in the early 1980's before passage of the anti-paraphernalia laws. Its performance was investigated in an unpublished study for the manufacturer by a graduate research assistant at MIT (Herms 1978). Although the Tilt is no longer available, the study report provides good evidence for the feasibility of vaporization.

The Tilt consisted of a wire sample screen mounted 5 mm above an adjustable 80-watt radiant heater, all encased in a plastic chamber with an exit port near the top (Diagram 1). In the study, samples of unpowdered cannabis buds and fragments were placed on the screen and held at constant temperatures

DIAGRAM 1. Tilt Advertisement

while the vapors were drawn off by suction. The lab reported that the Tilt achieved efficient vaporization at sample temperatures around 185-95°C. This is similar to the temperature range used by patients today. The sample exuded a thin stream of vapors, but kept its green color. Spontaneous combustion was reported at sample temperatures above 200°C.

Vapors from the Tilt were compared to smoke produced by similar samples combusted in a common clay pipe. THC and CBD were measured by capturing the smoke in a cold trap, dissolving the residues in acetone and methanol, and analyzing them via GC/MS. Tars were measured by capturing them in a Cambridge glass filter and weighing them. Carbon monoxide was detected by passing the smoke through a solution of palladium chloride, which precipitates palladium in the presence of CO.

The Tilt performed impressively, producing 79% less tar than the pipe while producing 80% more THC and 60% more CBD (Table 2). Unlike the pipe, the Tilt produced no detectable CO. The overall THC/tar ratio was improved by a factor of 8.5. The sizeable reduction in tars was evidently due to the absence of combustion, which forms hazardous quantities of PAHs at temperatures above 560-600°C (Wynder and Hoffmann 1967). Insofar as PAHs are thought to constitute the major carcinogenic hazard of smoking, the Tilt would seem to have offered substantial harm reduction benefits. Another remarkable feat of the Tilt was to generate more available cannabinoids than the pipe. The report speculated that this was because cannabinoids undergo degradative reactions such as polymerization, cyclization, etc., at combustion temperatures of 600° or more. However, a more likely explanation may be differences in combustion conditions, as observed in the Australian study.

NORML/MAPS VAPORIZATION STUDY

In order to further explore the potential of vaporization, California NORML and MAPS have undertaken a second, new vaporizer research project. The project is focusing on two models of vaporizers that are currently available and

TABLE 2. Pipe Smoke Compared to Vapor from Tilt Vaporizer

	Smoke from clay pipe	Vapor from Tilt
Delta-9-THC	0.044%	0.079%
Cannabidiol	0.015%	0.024%
"Tar"	16.5%	3.4%
Carbon Monoxide	Present	Absent

Adapted from Herms 1978

in use by medical marijuana patients: an electric radiator similar to the Tilt, and a hot air gun. The first phase of the project, a preliminary "proof of concept" study of the first device, is now complete. The results confirm that cannabinoid vapors can be generated around 185°C with substantial reductions in certain smoke toxins. Further studies are currently in progress.

The preliminary study tested a device called the M1 Volatizer (Figure 1), an aromatherapy device developed by Alternative Delivery Systems, Inc., consisting of an electric heating element arranged to radiate heat over a sample placed on a wire screen in a standard glass bong bowl. The sample consisted of sifted, cured sinsemilla cannabis (Figure 2). Temperature was regulated by a rheostat and measured via a themocoupled electronic thermometer on the sample. Vapors were drawn off with a vacuum pump and analyzed in three separate tests for: (1) carbon monoxide, (2) particulate matter, and (3) six target analyses: three cannabinoids (THC, CBD and CBN), and three toxic aromatic hydrocarbons, benzene, a known carcinogen, plus toluene and naphthalene.

Results showed that the vaporizer produced qualitative reduction in CO and particulates and complete elimination of the three toxic hydrocarbons (Table 3).

- Carbon monoxide was tested semi-quantitatively by drawing the sample for 20 seconds through a Drager tube. The M1 was operated at the comparatively low sample temperature of 170°C, where it produced a light gray vapor. Unlike the Tilt, the M1 produced detectable carbon monoxide (although the sensitivity of the Tilt CO test is unknown). When combusted with a match, the sample produced a thick, dark gray smoke. Unfortunately, the combustion test saturated the Drager tube, making it impossible to quantify the change in CO. The most that could be determined was that the M1 reduced CO by $\geq$33% compared to combustion.
- Particulate matter was measured by passing the smoke through a Balston Microfibre Disposable Filter Unit. The M1 was maintained at 185°C for 3 min and 45 secs and the vacuum pump run simultaneously for 5 min. A second sample was combusted with a match and the vacuum pump run for 5 min. The filter from the M1 showed slight discoloration at the top, while the filter from the combusted sample was saturated with yellow discoloration. The net particulate weight in the filter was at least 56% less using the vaporizer. Once again, however, it was impossible to measure the full extent of the reduction, since the combusted smoke appeared to have completely saturated the second filter.
- The three cannabinoids and three toxic hydrocarbons were measured by passing the vapors through a methanol-filled collection flask. The M1 was held at 185°C for three minutes and the vacuum pump run for 5 minutes. The control sample was combusted with a match with the vacuum pump running for three minutes. The contents of the flask were removed

> and assayed using a High Performance Liquid Chromatograph-Diode Array Detector-Mass Spectrometer. The three toxic hydrocarbons (benzene, toluene and naphthalene) were all detected in the combusted smoke, but not in the vaporized output. Unlike the Tilt, the M1 produced 85% less THC than combustion. There were indications that THC production could have been improved by refinements in laboratory technique. In any event, there was a 100% reduction in the toxin/THC ratio.

Data were insufficient to evaluate changes in CBD and CBN. (Users of the M1 have reported that they obtain different psychoactive effects at different temperatures, suggesting possible variations in the proportions of different cannabinoids.)

IMPLICATIONS FOR RESPIRATORY HARM REDUCTION

Results so far are tentative and incomplete, but promising. Clearly, much work needs to be done to explore the effects of different adjustments and smoking conditions. NORML and MAPS are currently sponsoring more research to determine how temperature affects the production of THC and other cannabinoids relative to other toxins. Tests indicate that small amounts of THC may be released at temperatures as low as 140°C. Significant amounts of

FIGURE 1. M1 Volatizer

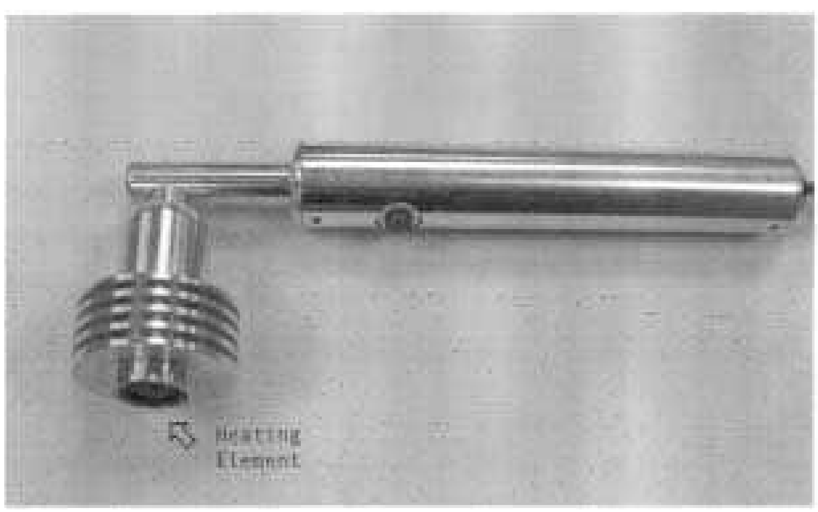
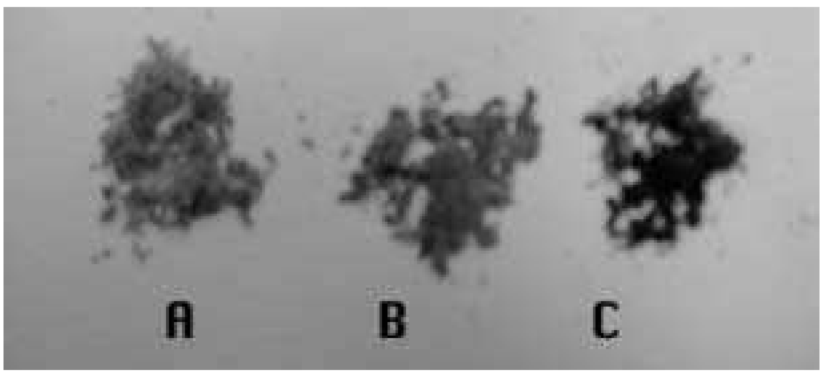


TABLE 3. M1 Vaporizer Performance: Reduction in Presence of Compounds Under Vaporization at 185°C Relative to Combustion

	Particulate "Tar"	Benzene	Toluene	Naphthalene	Carbon Monoxide*	THC
Reduction	> 56%	100%	100%	100%	> 33%	85%

*CO vaporization temperature 170°

FIGURE 2. Effect of Vaporization



A = Crude sinsemilla (olive green)
B = Similar specimen after vaporization by hot air gun at 180°C for ~5 min (brownish green)
C = Similar specimen after combustion (black)

benzene, toluene and naphthalene were observed above 200°C, and combustion occurred at temperatures of 230°C or higher. Further work is necessary to ascertain how these temperatures vary for samples of different humidity, potency, composition, and consistency. It is reasonable to assume that the vaporizer can completely avoid production of the highly carcinogenic PAHs, since these require pyrolysis to form. There is accordingly good reason to think that vaporizers can substantially reduce the presence of carcinogens in marijuana smoke. The question of carbon monoxide and other toxins is more uncertain. NORML and MAPS are seeking to explore these issues in future research. From the Australian work, it also seems likely that the performance of vaporizers and other smoking devices is critically dependent on the particular cannabis sample, its preparation and curing, variations in smoking technique, and other factors. These issues remain to be researched. In the meantime, vaporizers are becoming increasingly popular with medical cannabis patients, who report they are far less irritating than other methods of smoking.

Aside from vaporization, the one remaining strategy for cannabis smoke harm reduction is to use stronger THC preparations. Studies to date have found little evidence that users self-titrate dosage according to the potency of cannabis being smoked (Chait 1989; Zimmer and Morgan 1997). However, research has been restricted to a limited, low potency range (typically 0%-3%), using standard NIDA-issued leaf cigarettes. To date, no studies have been done with the kind of high-grade sinsemilla now widely available to patients through medical cannabis clubs, the potency of which may range from 8% to 20% or greater (Gieringer 1996). Lack of research in this area remains a grievous deficiency. The usefulness of high-grade sinsemilla for smoke harm reduction may be questioned in light of the Australian study, insofar as it indicates that differences in sample consistency and smoking conditions can be more important than the THC content of marijuana cigarettes. Nonetheless, patients widely report that they can effectively reduce smoke inhalation using high-quality sinsemilla.

The hazards of marijuana smoke may also be affected by the breathing pattern of the user. Some studies have suggested that prolonged breath holding does nothing to enhance the subjective effects of cannabis, but does increase absorption of carbon monoxide and other toxins (Azorlosa et al. 1995; Zacny and Chait 1991; Zimmer and Morgan 1997). However, other evidence indicates that breath holding does increase absorption of THC (Tashkin et al. 1991b). No clear-cut conclusions appear warranted at this point.

There is an evident need for further research on cannabis vaporization and marijuana smoke harm reduction. Sadly, due to the political fallout of the war on drugs, the government or leading private health research foundations are not supporting such research.

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Analgesic and Reinforcing Properties of ^{9}-THC-Hemisuccinate in Adjuvant-Arthritic Rats

Susan L. Broom
Kenneth J. Sufka
Mahmoud A. ElSohly
Samir A. Ross

SUMMARY. The use of ^{9}-THC hemisuccinate (HS) in a suppository formulation is an attempt to develop a cannabinoid possessing possible therapeutic effects with a minimal side effect profile. The purpose of this study was to investigate the antinociceptive and reinforcing effects of rectally administered ^{9}-THC-HS in rats. Tests were conducted in two groups of animals: Complete Freund's adjuvant-inflamed animals (CFA)

Susan L. Broom, MA, is Psychology Graduate Research Assistant, University of Mississippi, University, MS 38677.

Kenneth J. Sufka, PhD, is Associate Professor of Psychology and Pharmacology, University of Mississippi, University, MS 38677.

Mahmoud A. ElSohly, PhD, is Professor of Pharmaceutics, Research Professor, National Center for Natural Products Research, University of Mississippi, University, MS 38677, and is President, ElSohly Laboratories, Oxford, MS 38655.

Samir A. Ross, PhD, is Associate Professor of Pharmacognosy, Associate Research Professor, National Center for Natural Products Research, University of Mississippi, University, MS 38677.

Address correspondence to: Kenneth J. Sufka, PhD, Associate Professor of Psychology and Pharmacology, Peabody Building, University of Mississippi, University, MS 38677 (E-mail: pysufka@olemiss.edu).

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and non-inflamed controls. A hotplate test was administered to index hyperalgesia and possible analgesic effects of ^{9}-THC-HS on thermal nociception. CFA animals demonstrated shorter latencies than non-inflamed animals. The highest dose of ^{9}-THC-HS produced longer hotplate latencies. Additionally, the reinforcing properties of ^{9}-THC-HS were evaluated using the Conditioned Place Preference (CPP) paradigm. ^{9}-THC-HS produced an increase in preference scores in non-inflamed animals (positive reinforcement), but did not affect preference scores in CFA animals. These data suggest that ^{9}-THC-HS has therapeutic potential and is unlikely to possess an abuse liability when used in the context of chronic pain.

KEYWORDS. ^{9}-THC, adjuvant-inflamed, rat, hotplate, conditioned place preference

INTRODUCTION

The role of cannabinoids (CB) in pain modulation is well documented (Fuentes et al. 1999). Administration of anandamide, ^{9}-tetrahydrocannabinoid (^{9}-THC), and various selective CB receptor agonists, have shown antinociceptive effects in a variety of acute (Buxbaum 1972; Welch and Stevens 1992) and chronic (Sofia et al. 1973; Smith et al. 1998) models of nociception (for review see Pertwee 2001). These antinociceptive effects are mediated by CB1 receptors located at spinal (Yaksh 1981; Lichtman and Martin 1991; Welsh and Stevens 1992) and supraspinal sites (Lichtman and Martin 1991; Martin et al. 1993) as well as CB1 (Richardson et al. 1998) and CB2 receptors (Jagger et al. 1998) located in peripheral tissues (for review see Pertwee 2001). Although numerous studies suggest otherwise (Onaivi et al. 1990; McGregor et al. 1996; Sanudo-Pena et al. 1997; Tzschentke 1998), several experiments implicate cannabinoid systems in reward. For example, ^{9}-THC is self administered in humans (Chait and Burke 1994) and squirrel monkeys (Tanda et al. 2000), lowers intracranial self-stimulation thresholds in rats (Gardner et al. 1988) and produces place preference in rats (Lepore et al. 1995). ^{9}-THC has been shown to increase firing of dopamine neurons in the nucleus accumbens (Gessa et al. 1998), as well as increase dopamine levels in the shell of the nucleus accumbens (Tanda et al. 1997). Collectively, these studies suggest that CB reinforcement is likely mediated through the same

mesolimbic dopaminergic systems involved in opioid and psychostimulant reward (Koob and Bloom 1988). While one literature clearly suggests CB receptors present a viable target for analgesic drugs (for review see Pertwee 2001), a second literature suggests these putative analgesic compounds are likely to possess an abuse liability (Gessa et al. 1998).

Recent research indicates that the use of certain analgesics (e.g., morphine) that possess several liabilities (tolerance, dependence, etc.) may not be as controversial as previously suggested. Rats given repeated administration of morphine in the context of formalin-induced inflammatory nociception displayed less tolerance to morphine (Vaccarino et al. 1993; Bardin et al. 2000) and less severe withdrawal symptoms in response to a naloxone challenge (Vaccarino and Couret 1993; Bardin et al. 2000). In addition, rats given repeated administration of morphine in the context of chronic inflammatory pain induced by complete Freund's adjuvant (CFA) developed tolerance at slower rates and showed lower incidences of naloxone precipitated withdrawal symptoms (Lerida et al. 1987). Similar findings on tolerance and dependence have been observed clinically with opioid therapies (for review see Melzak 1991). Long-term use of codeine and oxycodone for chronic rheumatic conditions significantly reduced pain without requiring increased dosing except in cases where a worsening of the painful condition existed (Ytterberg et al. 1998). Collectively, these data suggest the liabilities of analgesics may be greatly reduced when these compounds are used in the context of pain management.

The medical use of cannabis for the treatment of chronic pain remains highly controversial. However, this controversy may be obviated by the development of the pro-drug ^{9}-THC hemisuccinate (^{9}-THC-HS) and its formulation as a suppository (Mattes et al. 1993). This formulation is but one solution to the undesirable inhalation route of cannabis administration. Moreover, rectal administration of ^{9}-THC-HS has been shown to produce a pharmacokinetic profile that is highly desirable for putative therapeutic agents. First, blood levels of ^{9}-THC and other CB metabolites do not show the rapid elevation typical of the inhalation route, which is commonly associated with euphoric effects. Second, blood levels of these constituents remain relatively stable for up to 6-8 hrs post administration (for review, see Walker et al. 1999). These pharmacokinetic factors, along with the notion that context is important in drug responses, suggest that ^{9}-THC-HS may not possess the reinforcing properties when administered in the context of chronic pain. To explore this possibility, the present study examined the antinociceptive as well as the rewarding properties of ^{9}-THC-HS in the complete Freund's adjuvant (CFA) model of chronic inflammatory pain.

METHOD

Place Preference Test

The conditioned place preference (CPP) paradigm (for review see Carr et al. 1989) is a procedure that is commonly used to evaluate the reinforcing and aversive properties of drugs (van der Kooy 1987). This paradigm is based on traditional learning principles and involves the pairing of a drug state with environments having distinctive stimuli (i.e., place). Following several drug-place pairings, an animal's preference is ascertained by examining approach responses to and maintenance of contact with the drug-paired environment. The CPP paradigm has become a frequently used method in behavioral pharmacology for examination of the positively reinforcing properties of abused drugs.

Male Lewis strain rats (100-125 g; Harlan, Indianapolis, IN) were housed in suspended steel cages (360 cm^2), maintained under a 12 hour light/dark cycle in a temperature controlled vivarium (22 1°C). Food and water were available *ad lib*. After a one-week acclimation period, animals received one week of handling exposure to reduce experimenter-related stress. Research protocols were approved by the Institutional Animal Care and Use Committee and were conducted under the ethical guidelines of the International Association for the Study of Pain (Zimmerman 1983).

The groups in this study formed a 2 × 3 factorial design that combined 2 levels of inflammation (CFA inflamed vs. non-inflamed) with 3 levels of drug (0.0, 2.5, or 5.0 mg/kg ^{9}-THC-HS). Sample sizes were n = 7 per group. Persistent unilateral inflammation was produced by injections of 0.1 ml of complete Freund's adjuvant (CFA: Sigma; St. Louis, MO) into the left hind paw (Butler et al. 1992). This model of arthritis produces long-lasting inflammation leading to hyperalgesia and joint destruction and bony proliferation of the metatarsal, tarsal, and ankle regions. Non-inflamed control rats did not receive this explicit manipulation. CFA was administered several hours after acclimation to the place preference apparatus.

^{9}-THC-HS (5 mg/kg/ml) or vehicle (Wacbee W) was administered immediately before the start of each conditioning trial (see below). Compounds were melted (45°C) prior to rectal administration to obviate the possibility of the animal evacuating a solid suppository. Pilot data examining plasma levels at various time points of rectal administration of melted ^{9}-THC-HS show that peak plasma ^{9}-THC levels were detected at 15 min post administration (approximately 110 ng/ml). This was followed by a gradual decline in plasma ^{9}-THC levels at 30 min (40 ng/ml); relatively stable ^{9}-THC levels were detected from between 60-360 min post-administration (15-25 ng/ml).

Six T-shaped place preference chambers were used in this study (see Sufka and Roach 1996 for details). The place preference procedure involved three phases consisting of one apparatus acclimation trial, eight drug/vehicle conditioning trials, and six discrete choice trials. The acclimation trial allowed animal access to the entire apparatus for a 15 min period one day before conditioning trials. The eight conditioning trials (1 per day of 60 minutes) consisted of counter-balanced, alternate-day pairings of drug (0.0, 2.5 and 5.0 mg/kg/ml) with the white compartment and vehicle (0.0) with the black compartment for a total of four pairings each. Drug preference was determined by the animal's choice behavior (i.e., first entry) to the drug-paired (white) vs. vehicle-paired (black) compartment on six discrete preference trials conducted two per day over a three day period and were conducted under drug-free states. From these choice measures, a single preference score was derived using the following formula: Preference Score = number of white compartment entries/6 (Sufka 1994).

Hotplate Test

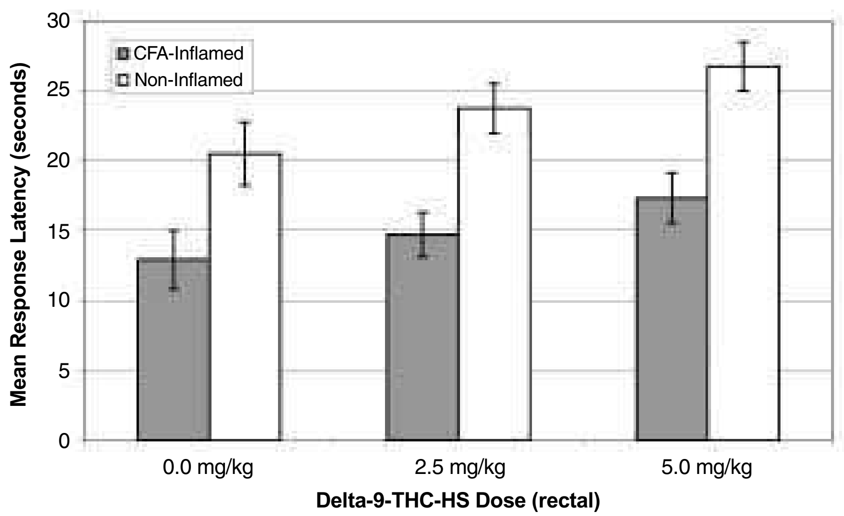
Tests of thermal nociception were conducted on the fourth day of drug exposure (Day 7 or 8 of conditioning trials). Rats were removed from the conditioning apparatus and placed on a hotplate apparatus with a surface temperature maintained at 50°C. Latency to lick a hind-paw served as the dependent measure. Animals that failed to exhibit a lick response in 30 seconds were removed from the hotplate and assigned a latency score of 30 seconds. Animals were euthanized at the conclusion of the experiment.

RESULTS

^{9}-THC-HS effects on thermal nociception are summarized in Figure 1.

Adjuvant-inflamed rats exhibited shorter response latencies than non-inflamed rats under the drug vehicle condition (i.e., hyperalgesia). In general, ^{9}-THC-HS increased latency scores for both groups compared to respective controls. A 2-way ANOVA revealed a significant main effect of inflammation $F(1,36) = 31.44$, $p = 0.0001$ and a significant drug effect $F(2,36) = 3.980$, $p = 0.03$. The inflammation × drug interaction term was not significant. Post hoc comparisons using Fisher's PLSD detected significantly shorter latency scores for CFA-inflamed animals compared to non-inflamed animals under vehicle condition ($p < 0.05$) (hyperalgesia). Further analyses revealed a significant increase in latency scores for the 5.0 mg/kg non-inflamed group compared to

FIGURE 1. Mean hotplate latency (SEM) as a function of ^{9}-THC-HS dose for CFA-inflamed and non-inflamed animals.



HOTPLATE DATA

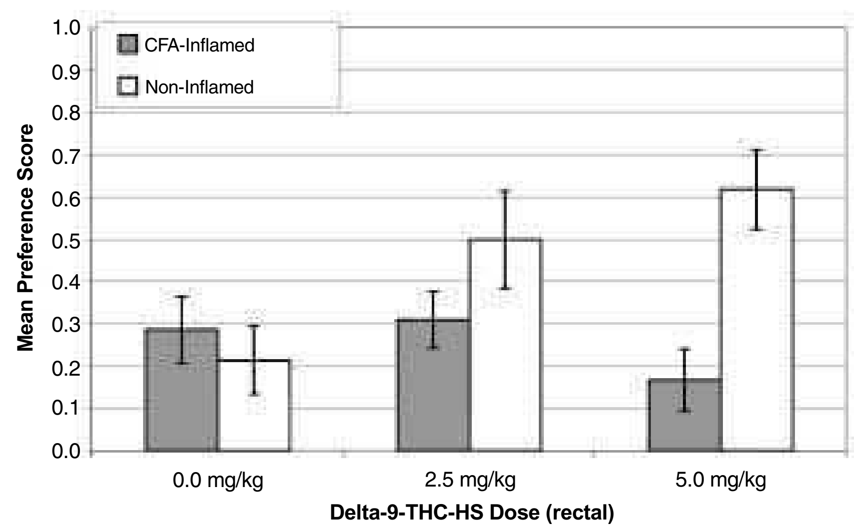
	Inflamed	**Non-Inflamed**
	Mean	Mean
0.0 mg/kg	12.90	20.49
2.5 mg/kg	14.71	23.74
5.0 mg/kg	17.32	26.77
	SE	SE
0.0 mg/kg	2.11	2.27
2.5 mg/kg	1.59	1.78
5.0 mg/kg	1.80	1.75

non-inflamed controls ($p < 0.05$). Although there was a trend in CFA-inflamed latency scores, no significant differences were observed. No further analyses were conducted on these data.

^{9}-THC-HS effects on preference scores for CFA-inflamed and non-inflamed animals are summarized in Figure 2.

Both groups showed a black compartment bias under the no drug condition. In general, ^{9}-THC-HS produced a dose dependent increase in preference scores in non-inflamed animals. However, this pattern was not seen in CFA-inflamed animals. Consistent with these observations, a 2-way ANOVA revealed a significant main effect for inflammation, $F(1,36) = 7.353$, $p = 0.01$, no

FIGURE 2. Mean preference scores (SEM) as a function of ^{9}-THC-HS dose for CFA-inflamed and non-inflamed animals.



CPP DATA

	Inflamed	**Non-Inflamed**
	Mean	Mean
0.0 mg/kg	0.29	0.21
2.5 mg/kg	0.31	0.50
5.0 mg/kg	0.17	0.62
	SE	SE
0.0 mg/kg	0.08	0.08
2.5 mg/kg	0.07	0.12
5.0 mg/kg	0.07	0.09

main effect for drug, and a significant inflammation × drug interaction, $F(2,36) = 4.634$, $p < 0.02$. Post hoc comparisons using Fisher's PLSD established no significant difference in baseline preference scores, indicating that the bias was present regardless of inflammation condition. Further post hoc analyses revealed a significant increase in preference scores for non-inflamed animals at the 2.5 and 5.0 mg/kg doses compared to vehicle controls ($p < 0.05$), indicative of cannabinoid positive reinforcement in these animals. However, for adjuvant-inflamed groups, preference scores were unaffected by ^{9}-THC-HS, suggesting that ^{9}-THC-HS lacks positively reinforcing properties in the context of persistent inflammatory pain.

DISCUSSION

While CB receptors present a viable target for pain management, the therapeutic use of cannabinoids remains controversial. However, an emerging literature suggests that analgesic drug liabilities can be diminished when these compounds are utilized in the context of pain management. These observations, along with the highly desirable pharmacokinetic profile of the suppository formulation of ^{9}-THC-HS, suggest that certain cannabinoids may provide for pain relief in some settings with little addictive liabilities. The purpose of the present research was to examine the putative antinociceptive and reinforcing properties of ^{9}-THC-HS in the rat adjuvant arthritis model of chronic inflammatory pain.

In the present study, adjuvant arthritic animals displayed shorter response latencies to a noxious thermal stimulus than non-inflamed controls. This hyperalgesic effect is consistent with reports of long lasting changes in nociceptive responses associated with CFA-induced arthritis (Lewis et al. 1985; Butler et al. 1992). While rectal administration of ^{9}-THC-HS tended to produce a dose-dependent increase in response latencies in both inflamed and non-inflamed groups, this antinociceptive effect was significant in only the non-inflamed animals. These findings are consistent with reports of cannabinoid modulation of thermal nociception in acute models (Buxbaum 1972; Yaksh 1981; Welch and Stevens 1992), but inconsistent with reports of cannabinoid modulation of hyperalgesia in chronic inflammatory models (Sofia et al. 1973; Smith et al. 1998). However, recent research suggests that cannabinoid agonists may be more effective in preventing the development of hyperalgesia than attenuating it (Li et al. 1999a). It is also possible that higher doses of ^{9}-THC-HS are required to modulate the thermal hyperalgesia in this CFA model of chronic inflammation. Finally, subsequent power analyses assuming a large effect size indicated that a significant analgesic effect would have been detected at the 5.0 mg dose in inflamed animals with the addition of as few as 7 animals per cell.

In the conditioned place preference test, both non-inflamed and CFA-inflamed animals that received vehicle in both conditioning compartments displayed a black compartment preference (i.e., preference scores under 0.5). This is not an unexpected finding and it is the principle reason for pairing all drug conditioning trials with the white compartment (i.e., condition against a black compartment preference). These baseline preference scores in vehicle-treated animals did not differ significantly between inflammation groups.

In non-inflamed animals, rectal administration of ^{9}-THC-HS produced a significant dose-dependent increase in place preference scores, a pattern of effects indicative of reward (for reviews see van der Kooy, 1987; Carr et al. 1989). These findings add to a literature that is considered equivocal at best on

the reinforcing properties of cannabinoids (see Tzschentke 1998 for review). For example, Mallet and Beninger (1998) report that in Wistar rats anandamide failed to produce place preference while ^{9}-THC produced place aversion. Place aversion has also been reported in Lister hooded rats using either CB receptor agonists or ^{9}-THC (Cheer et al. 2000). In contrast, cannabinoids produce place preference (when using a similar procedure and comparable doses) in Long Evans rats (Lepore et al. 1995), are self-administered in squirrel monkeys (Tanda et al. 2000) and produce lower thresholds for intracranial self stimulation in Lewis strain rats (Gardner et al. 1988). While the use of various animal models and paradigms may contribute to such equivocal findings, a growing literature suggests that strain differences in drug sensitivity may be an equally important methodological consideration (for review see Mogil 1999). Lepore et al. (1996) report that in an intracranial self stimulation paradigm, Lewis rats, which we used in the present study, are much more responsive to the rewarding properties of ^{9}-THC compared to Fischer 344 and Sprague-Dawley rats.

In contrast to non-inflamed groups, CFA-inflamed animals given rectal ^{9}-THC-HS did not show significant changes in their place preference scores, a finding that suggests an absence of drug reward in these groups. This finding is somewhat surprising in light of studies that demonstrate analgesic drugs produce place preference though their negative reinforcing properties (i.e., pain reduction) in models of chronic pain (Sufka 1994; Sufka and Roach 1996). However, one requirement for an analgesic drug to possess negative reinforcing properties is that it be sufficiently potent in reducing inflammatory nociception. While rectal administration of ^{9}-THC-HS significantly affected thermal nociception in non-inflamed animals, it was only modestly analgesic in attenuating thermal hyperalgesia in the CFA model of chronic inflammation and, therefore may not possess the necessary negatively reinforcing properties to support place preference. Given that ^{9}-THC-HS does not possess the same reinforcing properties in inflamed groups as it does in non-inflamed controls, we suggest that context can be an important determinant in drug responses.

To our knowledge, this is the first study assessing both the analgesic and reinforcing properties of cannabinoids in the context of chronic pain. While the finding that animals in persistent pain show less analgesia and reward have been interpreted by some to suggest accelerated tolerance (Gutstein et al. 1995; Li et al. 1999b), this interpretation is unlikely. Animals in the present study received low doses of ^{9}-THC-HS and on alternate day exposures, a procedure highly unlikely to produce tolerance. A more likely explanation is that the context in which drugs are employed is an important determinant in drug effects. Bardin et al. (2000, p. 61) have suggested, "that theories of (opiate) tolerance, withdrawal, and reward should incorporate the effects of pain." For example, opioid agonists given repeatedly in the context of persistent or chronic

pain show reduced tolerance, physical dependence and withdrawal while maintaining analgesic efficacy (Lerida et al. 1987; Vaccarino and Couret 1993; Vaccarino et al. 1993). The results of the present study are consistent with these findings and extend the importance of context to include cannabinoid systems and reward behaviors. Further studies evaluating therapeutic compounds should consider the context as an important determinant in drug response.

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Prospects for New Cannabis-Based Prescription Medicines

Brian A. Whittle
Geoffrey W. Guy
Philip Robson

SUMMARY. Cannabis is now emerging from a period of prohibition and being revisited as a potential source of treatments for conditions ill served by synthetic substances. Previous research focussed primarily on effects produced by synthetic cannabinoids such as THC, or cannabis of unknown cannabinoid content. Chemovars of cannabis characterized by high content of specific cannabinoids (primarily, but not only THC and CBD) have been developed. Clinical research using defined extracts from these chemovars is now underway in the UK.

Many diseases are multifactorial; a variety of receptors need to be targeted to produce a therapeutic effect. A defined botanical may better achieve this than a single synthetic compound as the components can act synergistically. A new generation of cannabis based medicinal products takes advantage of increasing understanding of the mode of action of cannabinoids, evidence-based research on clinical uses and new technology for realization of products, in anti-diversionary presentations. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]*

Brian A. Whittle, Geoffrey W. Guy and Philip Robson are affiliated with GW Pharmaceuticals Ltd., Porton Down Science Park, Salisbury, Wiltshire, UK SP4 0JQ.

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PROSPECTS FOR NEW CANNABIS-BASED PRESCRIPTION MEDICINES

There is nothing new about cannabis as a prescription medicine. The use of cannabis by mankind is probably as old as the need for pain relief but the use of cannabis as a prescription medicine is complicated by its alternate use as a recreational drug, and attempts to regulate that practice. The novelty described in this article arises from a re-examination of some historical uses of cannabis in the light of new technology. Research on possible modes of action of cannabinoids, and novel methods of administration have prompted a re-evaluation of the therapeutic benefit of cannabis and cannabinoids.

A distinction has to be made between the cultivation of hemp, which is primarily used for textile fibre and oil seed on the one hand, and cannabis, which is used for medicinal purposes on the other. Botanists are still debating whether *Cannabis sativa* and *Cannabis indica* are two species within the family Cannabaceae, or whether there is only one species with great diversity. The various uses of *Cannabis* spp. arise from crosses and selective breeding of varieties from various landraces. The plasticity of the cannabis genome provides opportunities for rational investigation of cannabis by providing defined chemovars. The availability of specific chemovars (varieties distinguished by the active constituents which they contain rather than fine differences in morphology) provides the test materials to cater for the current resurgence of interest in the therapeutic benefit of cannabis-based medicines.

The first edition of Merck's Manual (1899) reflects the important place that cannabis-based medicines had in the armamentarium of physicians at that time. At the end of the 19th century the majority of active drug substances were *materia medica* of plant origin. It is interesting that cannabis-based medicines provided treatments for conditions which, during the pharmaceutical revolution over the last half-century, have come to be catered for by synthetic drugs such as the benzodiazepines and potent synthetic analgesics. In Merck's Manual, preparations of cannabis are recommended as a hypnotic sedative which is very useful for the treatment of hysteria, delirium, epilepsy, nervous insomnia, migraine, pain and dysmenorrhoea. It is worth remembering that at that time, the available hypnotics were bromides, extracts of valerian and opium. Apparently, extracts of cannabis were prescribed for Queen Victoria, and in Victorian times, cannabis was a respectable and useful component of prescribed medicines. It continued in use until the middle of the 20th Century

but social abuse caused a re-think on the risks perceived to attend its use. Its use as a prescription medicine was reduced and finally prohibited by legislation.

The renewal of interest in cannabis-based medicines may lead to treatments for conditions which cannot be adequately treated by the best available medicines based on synthetic compounds. It is therefore vital that introduction of cannabis-based medicines is justified on the grounds of evidence-based medicine.

The use of cannabis as a recreational substance has resulted in the classification of cannabis as a Schedule I drug in the USA. Corresponding proscriptive legislation has been enacted by other signatories to the United Nations Single Convention. This reflects the regulatory attitude that it is a drug of potential abuse with no therapeutic benefit. In order to show that cannabis-based medicines have therapeutic benefit it is necessary to carry out clinical research. In order to carry out clinical research it is necessary to have a license to possess cannabis for research purposes. Although such licensing is theoretically possible, it has not until now been considered expedient to support research into the clinical usefulness of cannabis. Since 1971, the type of research that has received most support in the USA has been directed towards demonstrating the risks and hazards of taking marijuana. Research into its therapeutic benefit has not been practically possible or politically correct until very recently.

The House of Lords Science and Technology Sub Committee report (2001) gave very positive encouragement to carry out clinical research in the UK. With the support of the UK Home Office and the Medicines Control Agency (MCA) clinical research is now underway in the UK in patients with pain and associated with Multiple Sclerosis (MS), other neuropathic pain, and cancer pain unresponsive to opioids.

During the last three decades the main avenues of research have been preclinical investigations into the mode of action of cannabinoids and cannabinoid-like compounds. Clinical research has focused on the effects (mostly adverse events), which follow from use of marijuana either in smoked or orally ingested form. The majority of work on cannabis in the USA has employed a variety of cannabis that contains delta-9 tetrahydrocannabinol (THC) as the principle cannabinoid. In America and the Caribbean, there has been selection of plant varieties that produce maximum psychotropic effects, and this material contains only a small proportion of cannabidiol (CBD). In contrast, street material in Europe contains proportionately more CBD (about equal quantities of THC and CBD). This type of cannabis is referred to as "Moroccan"; it is grown in many European and Mediterranean countries.

Cannabidiol was formerly regarded as an inactive constituent of cannabis (Merck Index 1996), but there is now evidence that it has pharmacological activity, which is different from that of THC in several respects. In some cases it

appears that the pharmacological effects are different in sign, and that a combination of the two cannabinoids has therapeutic benefit not evidenced by either cannabinoid alone. In the case of cannabis there is evidence from clinical studies, and a strong patient perception that the ceiling of effect produced by extracts is greater than the effect produced by the corresponding amount of THC as a pure chemical substance (Price and Notcutt 1998).

In a regulatory climate where the emphasis is on new chemical entities, it is refreshing to see that the idea of using cannabis as a "botanical" extract is attracting serious attention. It means that clinical investigators can use a defined extract rather than a mixture of synthetic cannabinoids as the test object. Many of the reports of early work on cannabis are based on observations of subjects who smoked marijuana. Unfortunately, in the majority of these reports a clear understanding of the content of the major cannabinoids is lacking. The availability of cannabis with a pedigree and provenance allows for this variable to be controlled rigorously.

There are therefore a number of issues that need to be addressed in rehabilitating cannabis, first of all for some of its historic indications, and also for newer indications especially those areas where cannabis has a unique contribution. Among these are its use in the field of opioid-resistant pain in neurological conditions such as multiple sclerosis, cancer pain and migraine, and as an appetite stimulant in AIDS syndrome. In order to do this it is necessary to revisit the regulatory and statutory requirements for cannabis-based medicines. The major issues are:

- the concept of cannabis-based medicines as botanicals as opposed to pure cannabinoids;
- selective breeding of high yielding chemovars that produce an abundance of one particular cannabinoid;
- investigation of the pharmacological properties of various cannabinoids, i.e., cannabis is not just THC;
- variability of composition of cannabis. The geographical and genetic basis for variation in cannabinoid content of cannabis biomass and its control to give a standardized product;
- the quality aspects of cannabis biomass production;
- routes of administration and optimization of formulations to achieve particular pharmacokinetic profiles;
- regulatory issues, including health registration, and international legal requirements;
- security packaging and anti-diversionary devices which can be used in connection with cannabis-based medicines in order to satisfy statutory requirements.

THE RATIONALE FOR USE OF CANNABIS EXTRACTS

The pharmaceutical revolution in the 20th Century has been built on the concept of treating disease as a target that can be hit with a defined chemical compound. The discovery of receptors in tissues to which drugs bind, and in which they initiate a biological effect gave support to this idea. It is ironic that the concept of the "magic bullet" came to be understood in terms of targeting "receptors." With the advent of cloned receptor proteins it is now possible to show that a variety of targets may need to be hit in order to effect a therapeutic benefit. It seems likely that what is needed is a broadside rather than a sniper's bullet to despatch the pathological lesion. It is true that some diseases are the result of a single biochemical defect, for example the congenital absence of a particular enzyme system in phenylketuronia, but the majority of disease processes are multifactorial and have to be tackled holistically. Pathological lesions, where they can be considered as causative, require a number of therapeutic agents, or a single chemical with several properties, to achieve an improvement in the patient's condition. Plants contain a variety of active and adjuvant substances, and by a process of selection those that are clinically beneficial have become accepted as *materia medica*. Humans have been exposed to these complex mixtures for millennia. Those that are useful have been selected, and it is hypothesized that they present less of a metabolic shock than synthetic new chemical entities. In practice it has been found that extracts of cannabis provide greater relief of pain than the equivalent amount of cannabinoid given as a single chemical entity.

POLYPHARMACY

In medical education over the last half century, polypharmacy has been frowned upon. It was considered desirable in an age when new chemical entities were discovered with precise effects on biological systems and even particular receptors that these "clean" chemicals could be used to treat pathological lesions with surgical precision. Unfortunately, human disease has multiple pathologies and is rarely treatable with a single chemical agent. By default, a number of new chemical entities are used in order to treat different aspects of the patient's condition holistically. In plant extracts accessory constituents may produce an effect that is synergistic with the principal one. Others may mitigate side effects produced by one drug. By repeated use and empirical observation, these processes have selected the *materia medica* that are most useful and safe. Polypharmacy is a defining characteristic of most systems of traditional medicine, but it is sometimes overlooked that combination of agents in complex prescriptions was common in the UK until the third quarter of the 20th Century. The reasons for using combinations of *materia medica* as

active ingredients in Western prescriptions were four-fold. The prescription typically contained a principal active ingredient, a secondary ingredient, which was thought to have an adjuvant effect, a substance that antagonized some of the adverse events, and excipients, which had a physical function in ensuring the stability and patient acceptability of the total prescription. This style of prescription was phased out in the second half of the 20th Century, with the end of extemporaneous dispensing in the UK. However, when a botanical extract is tested in a well designed trial it is possible to justify clinical research on the extract as it is. It may contain more than one active ingredient. However, if it is presented as a well-defined botanical drug it can be used as a drug substance in its own right. The requirements from a regulatory point of view are that the medication should have the same composition each time it is prepared and be stable. In the case of cannabis, the limited stability of some of the older galenic preparations may have been a factor in their falling out of use. Improved methods of selection of plants, care in growing and improved methods of analysis now provide materials which can be used confidently as drug substances in their own right.

EFFICACY

Mechoulam (1976) showed that many of the characteristic effects of cannabis are produced by ^{9}-tetrahydrocannabinol. The availability of synthetic THC prompted the investigation of this chemical entity as the active ingredient in pharmaceutical preparations. Dronabinol (Marinol) is available as soft gelatin capsules containing 2.5, 5 and 10 mg of THC. As a synthetic compound it falls outside the Single Convention on Narcotics and is available as a prescription medicine. It has been progressively moved from schedule I and is now in Schedule III. Dronabinol capsules have an indication as an anti-emetic and have also been shown to stimulate appetite in patients with AIDS. The oral route of administration for cannabinoids leads to slow and irregular absorption. Some of the variability in response and low therapeutic window may be inevitable consequences of giving the drug by this route. Perhaps of greater significance is the pharmacokinetic profile after administration. Once the capsule is swallowed it is committed, and one of the unfortunate adverse events following the use of Marinol is that the patients who are heavily sedated ('stoned'), have to wait until the effect wears off. Comparisons of the effect of preparations containing dronabinol with those containing an equivalent amount of THC in the form of a cannabis extract (Iversen 2000) have shown that the maximal therapeutic effect and incidence of adverse events is lower when the cannabinoid is given as extract.

A number of explanations have been offered for the lower incidence of side effects and the higher ceiling of cannabis extracts over synthetic cannabinoids. In cannabis-based medicines, the presence of other cannabinoids such as cannabidiol (CBD) is thought to have an antagonistic effect to some of the effects of THC, although CBD may sum with other THC effects. The basis for this explanation is illustrated in Table 1, which shows, in broad outline, the different pharmacological effects of THC and CBD. It is clear from this table that all of the effects of cannabis cannot be explained in terms of just one cannabinoid. It is equally true that combination of THC and CBD in the correct proportions can offer a product with a tailored pharmacological and therapeutic profile, and possibly a lower cost in terms of adverse events.

In a pilot pharmacological screening test (In-house report, GPA 002/000159 2000), CBD gave a positive effect in a maximal electroshock test, showed antinociceptive activity, *in vitro* inhibition of 5HT-induced contractions of guinea pig ileum, anti-inflammatory action in the rat paw oedema test (rat), antimicrobial activity (*in vitro*) and potentiation of hexabarbitone sleeping time. These pharmacological activities support the proposed use of a CBD-

TABLE 1. Comparison of Some Pharmacological Effects of THC and CBD

Effect	THC	CBD	Reference
CB1 (Brain receptors)	++		Pertwee et al., 1998
CB2 (Peripheral receptors)	+	−	
CNS Effects			
Anticonvulsant†	−−	++	Carlini et al., 1973
Muscle Relaxant	−−	++	Petro, 1980
Antinociceptive	++	+	
Catalepsy	++	++	
Psychotropic	++	−	
Antipsychotic	−−	++	Zuardi, 1997
Neuroprotective Antioxidant Activity*	+	++	Hampson A J et al., 1998
Antiemetic	++	−	
Sedation (reduced spontaneous activity)	+	+	Zuardi, 1997
Cardiovascular Effects			
Bradycardia	−−	+	Smiley et al., 1976
Tachycardia	+	−	
Hypertension§	+	−	
Hypotension§	−	+	Adams et al., 1977
Anti-inflammatory			Brown, 1998

* Effect is CB1 receptor independent.
† THC is pro convulsant.
§ THC has a biphasic effect on blood pressure; in naïve patients it may produce postural hypotension and it has also been reported to produce hypertension on prolonged usage.

rich cannabis extract in the treatment of severe arthritis (Burstein and Raz 1972).

QUALITY ISSUES

There is a compelling case for development of cannabis-based medicines using defined extracts as the active substance. GW Pharmaceuticals has developed a growing system that builds in quality by excluding the majority of adventitious factors, which normally have to be monitored and tolerated in field grown crops. Standardization and high quality have been achieved by growing specific chemovars under controlled conditions. However compelling the case for botanical extracts, it is essential that quality be built into the product. In order to do this it has been necessary to examine critically every aspect of the growing and production process. Field grown crops are subject to a range of factors adversely affecting quality. Recently, guidelines have been proposed for Good Agricultural Practice, expected to be incorporated into European Union (EU) legislation. These guidelines address many of the issues applicable to field grown crops. However, a more radical approach, giving an even higher degree of regulatory assurance, is to protect the plants from as many adventitious factors as possible by growing under glass in a controlled environment.

BOTANICAL SOURCE OF MEDICINAL CANNABIS

Hortapharm BV and GW Pharmaceuticals have produced a range of cannabis chemovars, which express a high proportion of their cannabinoid content as a specific chemical entity. This library contains chemovars that produce predominantly either THC, CBD, one of their precursors or congeners. This opens up the exciting prospect of using chemovars that produce some of the less well-studied cannabinoids such as tetrahydrocannabivarin (THCV) and cannabinodivarin (CBDV), which are characteristic of cannabis grown in South East Asia. The use of extracts from specific chemovars makes it possible to examine the effects of single extracts, or by blending extracts, to achieve a ratio of cannabinoids which may be optimal for a particular therapeutic condition. Initially, extracts from a high THC and a high CBD chemovar have been used to produce medicinal cannabis products. These contain predominantly THC, predominantly CBD or a defined ratio of THC and CBD.

The high THC chemovar is a stable hybrid of *Cannabis sativa*, subtype *indica* crossed with *Cannabis sativa*, subspecies *indica*. The principal cannabinoid produced (typically more than 94% of the total cannabinoid) is ^{9}-tetrahydrocannabinol with approximately 1.5% of cannabidiol.

The high CBD chemovar is a stable hybrid of *Cannabis sativa*, subtype *sativa* that has been heavily crossed and inbred with other varieties of *Cannabis sativa*. Typically, the principal cannabinoids produced in this chemovar have more than 90% of total cannabinoid as CBD, with approximately 3% present as THC. The exact details of the pedigree of these chemovars are the subject of Plant Breeders' Rights.

After selection for cannabinoid content, a group of chemovars is produced, but not all of them are equally hardy and suitable for volume production of cannabinoids. The plants are further selected for vigour and robustness. The production of standardized cannabis is from cuttings prepared from "mother" plants. This ensures that the genotype is fixed and there is consistency in the proportion of cannabinoids in each chemovar. Stability of cannabis biomass is also improved in these chemovars. Production quantities of cannabis are produced from seedless female plants.

Cannabis is a dioecious plant, and it is thus typical for male and female flowers to appear in separate plants. The male plant bears staminate flowers and the female plant carries pistillate flowers, which develop into the fruit and seeds. The content of useful cannabinoid is greatest in the flowering heads, particularly in the female plants. Monoecious plants may occur bearing both male and female flowers on different branches of the same plant. The appearance of male flowers results in early fertilization of female plants, with loss of yield. To optimize cannabinoid content it is essential to remove these "rogue" male flowers before they mature. Monoecious plants appear spontaneously in medicinal cannabis plants but are more frequent in varieties intensively bred for hemp production. In production of cannabis, the appearance of male flowers will result in fertilization of female plants, and reduction in yield of cannabinoids. For this reason plants bearing male flowers are removed as soon as they are detected. Raman (1998) has reviewed the process of masculinization of female plants in order to produce "self-varieties." Masculinization of female plants can be induced by chemical agents in order to produce self varieties for selective breeding (Ram and Sett 1982). A number of agents are known to induce masculinization including irradiation, treatment with streptovaricin and exposure to low levels of carbon monoxide.

Using a variety of techniques, De Meijer and Keizer (1996) have produced specific chemovars that have a very high content of total cannabinoids expressed as either THC or CBD. This programme of work has resulted in other chemovars that predominantly express cannabinoid content as specific cannabinoids other than THC and CBD.

In addition to fixation of the chemovars in terms of cannabinoid expression, it is necessary to further select for vigour. This has resulted in a series of chemovars that have the necessary robustness for large-scale production of cannabis in controlled conditions of lighting and temperature. This is the es-

sence of the technology that has been developed by Hortapharm BV and GW Pharmaceuticals, after selection from accessions of material obtained from around the world.

The original (mother) plants are maintained in long day length to produce non-flowering, vegetative growth. The mother plants are used as a source of genetically identical cuttings (also referred to as clones). The clones are then grown on, and by manipulation of day length they are induced to flower and produce plants from which the product is prepared. A percentage of the young clone plants, when established, are retained under vegetative conditions (not allowed to flower) to produce further clones. The two chemovars used in the production of cannabis-based medicinal extract were selected from the range of varieties produced in this programme.

In the plant, cannabis resin is present in glandular trichomes. It is possible to obtain fractions containing a high concentration of resin by collecting these. Fractions rich in these trichomes constitute hashish, which may contain up to 60% of cannabis resin. However, for volume production it is more economic to harvest whole plants when the flowers are beginning to senesce, and to extract cannabinoids from the entire aerial parts of the plant.

HARVESTING

Field grown cannabis, if allowed to fall on the ground, is subject to fungal attack and contamination from birds and vermin. When grown on the small scale it is possible to hand pick the flowering tops from cannabis, but volume production demands mechanized means of harvesting and processing. When harvested, cannabis has moisture content of approximately 25%. In order to have a stable product it is necessary to reduce the moisture content to under 12%. Biomass stored away from light and heat is relatively stable. In the dried plant, a significant proportion of total cannabinoid is present as the cannabinoid acids (THCA and CBDA). These acids are not known to have cannabinergic activity and conversion of cannabinoid acids to free cannabinoids, the biologically active form, occurs spontaneously over time and is accelerated by heating. Smoking effectively decarboxylates cannabinoid acids. In other methods of preparation for medicinal use, it is necessary to ensure that this change is effected, as the cannabinoid acids do not have biological activity.

PREPARATION OF EXTRACTS

Historically, extracts of cannabis were prepared (BPC 1934) by percolation with 90% ethanol. Various galenical preparations have been used, including tinctures (ethanolic extracts). Solid extracts (solvent-free) have been used for

preparation of finished dosage forms after the optional removal of solvent. The extract of cannabis is an oily resinous material, which is virtually insoluble in water.

Other solvents that have been used in an attempt to produce a purified extract of cannabis include fluorinated solvents such as heptafluropropane (HFA 227) and norflurane (HFA 134a). These solvents produce extracts that contain waxes and colouring agents, and a small amount of terpenes in addition to the cannabinoids.

A cleaner extract is produced by extraction with supercritical CO_2. In this process the majority of colouring matter and chlorophyll are left behind. The extract contains principally the cannabinoids but also some high molecular weight waxy ballast and sufficient terpenes to produce the characteristic scent of cannabis. Most of the ballast can be removed by chilling an alcoholic solution, a process referred to as “winterization.” The winterized extract is an accessible material for production of liquid dosage forms using pharmaceutically acceptable solvent systems.

CHOICE OF DOSAGE FORM

Cannabis preparations have been administered by most routes commonly employed in the pharmaceutical industry. Historically, it was given in mixtures prepared from tinctures, and in the form of pills. In Victorian times plasters prepared from powdered drug were applied locally to relieve pain and with ointments represent the first attempts at transdermal application. Oily eye drops were also used for the treatment of glaucoma. Smoking is probably the fastest way of producing the pharmacological effects of cannabis in humans after intravenous injection. However effective as a mode of recreational use, smoking as a route of dosing for a prescription product can no longer be justified on ethical, medico-legal or safety grounds.

The sublingual route administration has shown a rate of absorption intermediate between that achieved by smoking and the oral (swallowed) route. Selection of a dose presentation based on extracts containing THC and CBD has produced a medicine that is organoleptically acceptable to the majority of patients. More importantly, the ability to take the medicine in small sub-doses has been invaluable in the investigation of efficacy and safety. The time course is such that the patient is able to take account of cognitive cues in timing the next dose increment. This allows patients to titrate the dose to a level where they achieve benefit and minimize unwanted side effects.

Recreationally, smoking is the commonest route of administration, closely followed by oral ingestion (brownies). Some patients with multiple sclerosis who smoke cannabis report relief of spasm and pain after the second or third

puff of a cannabis cigarette. This implies very rapid transit to, and absorption into the central nervous system. The time involved is seconds rather than minutes. The oro-pharyngeal, buccal, sublingual and respiratory mucosae have venous drainage directly into the *vena cava* and the left side of the heart. Material absorbed through the mucosae of these areas is therefore not exposed to the liver during its first circuit into the systemic circulation. The drainage from the rest of the gastrointestinal tract (other than for the distal part of the rectal mucosae) perfuses the liver, the major detoxifying organ of the body. In addition to protecting the organism from ingested toxins, the liver also metabolizes medicaments, which are subject to the same chemical processes. Blood from the liver subsequently returns to the left side of the heart and reaches the rest of the systemic circulation. This first pass through the liver may result in the removal of a substantial proportion of an ingested medicament. In the case of cannabinoids, more than 95% of an ingested dose is metabolized during this first pass. This may contribute to the variability and timing to achieve maximal plasma concentration (C_{max}) and the time to achieve this maximum (T_{max}). In the case of cannabis there is a very wide variation in the values of C_{max} and T_{max} observed. A further complication is the rapid metabolism of tetrahydrocannabinol to 11-hydroxy-THC, which is also psychoactive. This occurs during the first pass through the liver and possibly through other tissues involved in the chain of absorption before cannabinoids reach the left side of the heart.

The areas of the respiratory/alimentary system having venous drainage into the systemic circulation, thus avoiding the first pass effect, are the mucous membrane of the buccal cavity, the sublingual area, the oro-pharynx, the respiratory tract, and the distal part of the rectum. The avoidance of the first pass effect is the rationale for the use of buccal, nasal, sublingual and suppository formulations. Each has advantages and disadvantages.

- Suppositories are subject to hygienic and patient compliance restriction.
- Formulations intended for administration to the nasal mucosae may cause pain or reflex sneezing, and in extreme cases cause irritation (Tashkin et al. 1973) and damage to the mucosae.
- Preparations intended for administration by inhalation have the advantage of speed of onset, but there is a direct irritant effect of THC *per se*, in addition to the irritant effect of the products of pyrolysis. Opinion is divided on the direct irritant effect of cannabinoids and it is possible that formulations that contain particles capable of being hydrated in their transit of the respiratory tract have lower irritancy.
- Sublingual formulations may stimulate the flow of saliva, and it is difficult for patients to avoid swallowing when substantial amounts of saliva are produced. If drugs applied to the sublingual mucosae are swallowed

the cannabinoids will be subject to the first pass effect and will therefore be less effective. This will result in proportionately higher levels of metabolic products.

- Buccal formulations where the product is held in contact with the parietal buccal membrane may be subject to the same limitations. Both sublingual and buccal formulations depend on the efficient transfer of medicament from a hydrophilic vehicle to the cell membrane of the sublingual or buccal mucosae. It is likely that absorption of cannabinoids takes place through the interstices in the membranes or by transfer into the epithelial cells. This transfer is governed principally by the lipid solubility of medicaments, and the partitioning of a lipid solid drug through an aqueous surface layer into a lipophilic absorption mechanism is an area for investigative research.

There are therefore a number of physical and biological limitations on the routes of administration of cannabinoids, but also opportunities for innovation in devising presentations to optimize administration. With the development of sensitive and specific methods of analysis, it is now possible to produce the kinetic profile that is best suited to treatment of specific therapeutic indications. Sublingual administration gives slower absorption than the respiratory route. However it is fast enough. The interval between doses allows time for subjects to become aware of the onset of cognitive changes in relation to wanted effects. Patients are thereby able to titrate doses to exploit the window between wanted therapeutic effects and unwanted side effects.

CLINICAL STUDIES

Initial phase 1 studies were carried out using a glycoalcoholic solution of cannabis extract, which was applied to the sublingual mucosae (Guy, Whittle and Grey 2000a and Whittle and Guy 2001). Fractional doses were given so that 2.5 mg was applied at intervals of 10 minutes.

The first human exposure to GW Pharmaceuticals (GWP) preparations of THC and CBD took place in healthy volunteers late in 1999. This placebo-controlled, six period, crossover study in six healthy volunteers assessed pharmacodynamic effects, pharmacokinetic profile, safety and tolerability including examination of routine clinical laboratory results and continuous monitoring of ECG and vital signs, cognitive effects, adverse events and subjective effects of a single dose of three cannabis based medicinal extracts (CBME) administered sublingually, and one formulation via aerosol and nebulizer.

CBME tested were High THC, High CBD, THC:CBD 1:1 mixture, and matching placebo. Maximum permitted dose was THC 20 mg and/or CBD 20

mg given incrementally at 10-minute intervals. All six subjects successfully completed the six periods of the study without giving rise to safety concerns. Pharmacokinetic profiles showed reliable absorption of CBME with peaks at 5 minutes following inhalation and approximately 2 h sublingually. Well-recognized effects of THC such as psychoactivity, conjunctival reddening, and intermittent tachycardia were observed. Overall, the cognitive effects were modest. Adverse effects reported by the subjects included vivid dreams, conjunctival injection, tachycardia, postural hypotension, hunger, pallor and sweating. No serious adverse effects were noted.

The design chosen by GWP for the initial clinical research is a series of double-blind, crossover, placebo-controlled single case studies. After an initial two week run-in period on open label THC:CBD 1:1 mixture, subjects enter a four way double blind crossover study comparing the 1:1 THC:CBD mixture, High THC, High CBD and placebo. After completion of this, patients are given the option of entering a long-term safety and tolerability follow-up study.

Sixty-four patients with a range of medical diagnoses including multiple sclerosis, spinal cord injury and other serious neurological conditions, have so far been titrated on to sublingual CBME. Of these, over 80% have chosen to continue receiving the medication in the long-term extensions. Between them, these subjects have now generated more than 950 patient-treatment weeks.

Virtually all the subjects remaining on treatment have experienced significant alleviation of at least one key symptom, and in some cases the improvement has been sufficient, in the patients own words, to transform lives by dramatically reducing pain. These improvements are particularly notable in that an inclusion criterion is intractability of symptoms in the face of available standard therapy. Among the positive effects recorded are relief of neuropathic pain, spasms, spasticity and bladder-related symptoms; at least partial alleviation of tremor; and improvements in mood and measures of overall well-being. Intoxication is the most frequent dose-limiting effect for the THC-containing medicines.

Because so little is known of optimal dose patterns for CBME, patients have been allowed to establish dose level and frequency by self-titration, with defined upper limits (no more than eight 2.5 mg doses within any 3 h period and no more than 120 mg/24 h). Many subjects chose to take small doses at more frequent intervals than the usual three or four times a day pattern. A wide range of individual daily dose requirements has been noted, but once a pattern is established very little variation within subject seems to occur. No evidence of tolerance to therapeutic effects has been noted so far. Most patients can achieve symptom relief at a sub-intoxication dose, although the margin between the two thresholds is often narrow.

A range of adverse effects has been reported, most of which seem to occur early in the treatment and diminish as a suitable dose is arrived at by self-titration. The most commonly occurring effects (i.e., those reported on 3 or more occasions) in descending order of frequency were headaches, nausea, burning in the mouth, intoxication, sweating, flu-like symptoms, vomiting, falls, and chest pain of unknown origin. Almost all of these effects have been transient, of only mild or moderate intensity, and well tolerated by the patients. One event defined as severe has been reported, but this ended in complete recovery following supportive treatment.

These pilot studies have provided important information which will inform future randomized, placebo-controlled cohort studies, including appropriate doses and dosing patterns, selection of CBME content for different conditions, identification of target symptoms and outcome measures. They have uncovered opportunities for optimization of the formulations (e.g., volume, solvents, taste, and blinding) and types of presentation, which can be incorporated into larger studies. With such small numbers, it is difficult to interpret the ultimate significance of adverse events. However, these preliminary studies have provided the investigators with invaluable hands-on experience of using cannabis-derived medicines in a therapeutic setting. They supplied further reassuring evidence of the safety and tolerability of these medicines in patients, often middle-aged or elderly, with serious medical disorders.

NON-SMOKING INHALATION

Non-smoking inhalation of cannabis is a fast and attractive route of administration for the new generation of cannabis-based medicines, which have been developed. The question arises, why not use smoking as a method of administration for a prescription product? The reasons are self-evident but are worth re-stating as this proposal periodically re-surfaces.

There are medico-legal implications involved in recommending smoking in any form. Cannabis, like other cellulosic materials, produces particulates and tar when burnt. These contain polyaromatic hydrocarbons (PAHs) known to be carcinogenic. The pattern of bronchial pre-carcinogenic cytological changes in habitual chronic cannabis smokers is similar to that of tobacco smokers. It is difficult to dissect out the contribution made by cannabis alone in this regard, since many cannabis smokers also smoke tobacco, and many study designs do not allow this variable to be assessed. Other factors that militate against the use of smoking as a route of administration for a prescription drug are the dislike of some patients for smoke and the perceived sociological disincentives expressed by some patients who do not wish to be seen smoking a street drug. Reports of an irritant effect of cannabis smoke are also a factor to be taken into

account. Recreational smoking is a personal decision and is vigorously defended by users as a personal right. However, in the present climate of opposition to smoking in general, drug developers are unwilling to shoulder the moral and legal responsibility for adverse events resulting from recommending it as method of administration. There is, therefore, a search for non-smoking methods of administering cannabinoids via the respiratory tract. A number of methods of administration currently in use for other drugs have been examined for their applicability to administration of cannabinoids or extracts of cannabis.

The physical properties of medicaments given by inhalation are important. When air is inhaled through the nose it passes through the naso-pharynx and past the epiglottis into the trachea. The naso-pharynx acts as a filter to prevent the entry of large particles and has a role in warming (or cooling in the case of smoking) and humidifying the stream of air and particles. Air passing into the trachea enters the lung via the bronchi, bronchioles and alveoli. The bronchi walls contain rings of cartilage linked together with smooth muscle. Their inner surface is lined by cilia, which beat and assist the upward and outward movement of unwanted fine particles, which are then swallowed. The bronchioles are narrower versions of the bronchi, which do not have cartilage but are elastic; they constrict and dilate to modify the resistance to passage of air. Deeper within the lung the bronchioles branch repeatedly giving rise to terminal bronchioles, and the end outgrowths of the bronchioles are the alveoli. The walls of the respiratory bronchioles and alveoli are thin, covered in a network of fine capillaries and are the sites for gaseous and drug exchange. Products given by inhalation usually deliver the active ingredient in the form of aerosol droplets or as solid particles. In the case of cannabis, some of these particles may be condensed from vaporized cannabinoid that have subsequently become hydrated in the high relative humidity within the bronchial tree. The site at which droplets or particles are deposited in the lung depends largely on their aerodynamic diameter. This measure is the diameter of the perfect sphere that would fall through air at the same speed as the particle. Particles with an aerodynamic diameter greater than 10 micrometers tend to be deposited in the upper regions of the respiratory tract where they are quickly removed by the ciliated epithelium. Only particles approximately 2 micrometers or less are capable of reaching the alveoli. In the case of conventional drug particle inhalers, it is estimated that only 5-20% of the delivered dose reaches its site of action.

The relative humidity of the respiratory tract is approximately 99.5%, and inhaled particles, may hydrate and grow in size. Aerosolized liquid droplets may behave similarly. An equilibrium is attained with this type of particle when vapour pressure on the surface of the particle and in the respiratory tract are the same. This process may take only milliseconds to complete. Particles with an aerodynamic diameter of less than 1 micrometer may also be re-expired. Particles with a diameter of less than 0.5 micrometers display Brownian

motion and a small fraction may be re-expired and lost. These factors are important in designing novel presentations of cannabis-based medicines for inhalational use.

The technology for producing aerosolized metered dose inhalers (MDIs) and drug-particle inhalers is well described, and attempts have been made to adapt this type of inhaler for delivery of cannabinoids. THC and CBD are virtually insoluble in physiological saline, but are soluble in high concentrations of ethanol. There are limits on the quantity of ethanol that can be taken into the respiratory tract. Vaporization of ethanol also produces both cooling and irritant effects. This greatly limits the amount of cannabinoid that can be administered per actuation of a pressurized device. Co-solvents such as propylene glycol and glycerol and surfactants produce marginal improvements in the concentration of cannabinoid, but a typical quantity that can be delivered (25-125 micro litres) using commercially available spray buttons is a trade off between solubility, volume and the irritant effect of the solvent.

VAPORIZERS

The challenge is to devise a vaporizer that produces the rapid effects of cannabis without the disadvantages of pyrolysed material and the consequent tar production. On the World Wide Web there are a number of sites where designs for vaporizers are posted. These consist of a source of heat, which is applied to a portion of cannabis herb, and a means for containing the volume of vapour, which is produced so that it can be inhaled in the stream of inspired air. Typically, the heat is applied in the form of an electrical heating element (soldering iron bit) or radiant heat from an incandescent light bulb. The fluidised bed principle has been applied in a device recently patented by Pate (1997). In this device a portion of cannabis herb is entrapped between two screens, and heated air is passed through the fluidised bed of cannabis and distills off the cannabinoids. The vapour so produced can then be inspired into the respiratory tract substantially free of particulates and smoke. Careful regulation of the temperature is necessary to ensure that distillation is carried out at a temperature below that at which cannabis pyrolyses.

Vaporizers, in which a concentrated extract of cannabis is heated to produce vapor, are under development. Electronic control of the energy applied to the heater ensures that the concentrated extract of cannabis is efficiently vaporized, without the production of pyrolysis products. The device generates the vapour during the course of a single inspiratory cycle in a manner intended to produce a profile of absorption in the patient similar to that obtained from a cannabis cigarette. The device is a portable self-contained unit, powered by rechargeable batteries and is controlled electronically. The control device has an

algorithm which computes the energy required to produce vaporization in the dosage form, and switches current to effect vaporization at a temperature below that causing pyrolysis. The generation of vapour from the portion of medicament is done in the course of a single inspiration. The equipment also has provision for recording the date and time of use.

Control of and recording of the pattern of use are important from the standpoint of security. The recording of data on usage is an important factor in giving confidence to enforcement agencies, and monitoring of the supply by the pharmacist. The technology also provides an opportunity for data collection in the context of clinical trials monitoring and patient compliance. The method of secure dispensing and the device are the subject of UK and overseas patents (Guy, Whittle and Grey 2000b). The secure dispensing features of the equipment include a tamper-evident membrane, matching of the patient with prescription and a frangible linear link. This ensures that if the device is improperly used it locks up completely and cannot be operated. In addition to the recording and read-out of data relating to use, a simple and robust exchange scheme has been set up with pharmacist-supervised control of replacement and extension therapy.

NEBULIZERS

Nebulizers are in use for the administration of antimicrobial drugs, bronchodilators, corticosteroids and asthma treatments such as sodium chromoglycate. Nebulizers rely for their efficacy on provision of doses of medicament over a relatively prolonged period at correspondingly low concentration. A feature of nebulization is that the nebulisate is carried on a mist of water particles. Many types of nebulizer are in use, and a characteristic of the designs is that a fine mist of particles is generated in a flow of gas that is saturated with water vapour. This last feature facilitates breathing by ensuring that mucous is thinned and the epithelium of the respiratory tract does not dry out. Considerable ingenuity has been exercised in devising methods for generating a mist of particles. These include devices using a Venturi effect. Essentially, this consists of a jet of gas blowing across the end of a dip tube, the other end of which rests in a reservoir of liquid. The reduction in pressure draws water up the tube that is then converted into a spray. Smaller particles are separated from those with a high mass and kinetic energy, which are returned to the reservoir for recycling.

In the Halolite™ nebulizer, medicament solution is drawn up the central part of a rotating hollow-stemmed "T" bar, which throws off particles centripetally. Particles with a high mass hit the wall of the chamber, drain down into the reservoir and are recycled. Smaller particles are aspirated in the stream of

inhaled air. This model of nebulizer has an algorithm that ensures that a portion of nebulisate is injected into the inspired air at a determined time. The amount of nebulisate retained within the respiratory tree by the use of this algorithm is in excess of 93%. Where the vehicle used contains volatile components it is necessary to make allowance for this as some fractionation may occur with variation in the amount of drug made available as nebulisate. The extent of lung deposition from different types of nebulizer is reviewed by Hardy, Newman and Knoch (1993).

Many commercial nebulizers are intended to provide a relatively low concentration of medicament, in a saturated atmosphere over a prolonged period of time. This is not the ideal for administration of cannabis. Smoked cannabis is rapidly effective and patients with MS report relief starting with the second or third draw. Davis, McDaniel et al. (1984), have described the complex changes occurring in a smoked marijuana cigarette. The amount of THC entering the respiratory system is probably in the range 5-10 mg of THC. An important characteristic of this type of administration is the pulsatile presentation of a discreet quantity of cannabinoid that allows the patient to discern cognitive effects following each draw. The patient can then regulate both the amount absorbed and rate of absorption. Patients with disabling pain claim that they can titrate the dose to obtain relief with the minimum unwanted cognitive effects.

The ability to achieve this window of therapeutic benefit without adverse events is also a difference between patients and recreational users. The object of non-smoking alternative methods of administration must be to mimic this pattern of delivery. A number of designs of nebulizer have been devised to increase the concentration of medicament in the nebulisate. Piezoelectric oscillators have been used to generate fine particles by forcing liquid through perforated plates into a stream of air or oxygen. This method of production results in a population of particles with a more uniform mass distribution. Ultrasonic energy can be used to produce a dense cloud of particles of uniform size, and there are proprietary devices based on this principle. A feature of this type of device is the rapid response made possible by switching electrical energy to the ultrasonic generator. This gives what is essentially a square wave function and the algorithm described in the secure dispensing patents (Guy, Whittle and Grey 2000b) can be used to control the rate and quantity of cannabinoid delivered during each respiratory cycle.

TRANSDERMAL ADMINISTRATION

Theoretically, the use of transdermal delivery systems for cannabinoids is attractive. The active constituents are lipid soluble, non-ionized, and of a molecular mass which is at the top end of the range normally considered feasible

for transdermal absorption. However, in practice the results have to date been rather disappointing.

One traditional and spectacular way of collecting hashish reported by Samuelsson (1992) is for the operative to run through a crop of flowering cannabis and to allow resin to adhere to clothing and skin. Cannabis resin, which adheres easily to the body, is then scraped from the clothing and skin. Exposure of skin to resin containing high concentrations of cannabinoids has not been reported to produce intoxication. This would indicate that absorption of cannabinoids transdermally without further formulation is not extensive. Nevertheless, there are a number of patents that claim that significant plasma levels can be achieved by transdermal administration. This illustrates the contribution made by presentation and formulation.

To speed absorption, a number of systems have been designed to enhance transdermal delivery by energizing transport. These include:

- the use of ultrasonic stimulation of the skin
- iontophoresis
- incorporation of cannabinoids into liposomes, which are then incorporated into transdermal patches.

A function of skin is to protect the internal organs from the environment, and in the case of cannabis and cannabinoids it appears to do this well. The routes of entry through the skin are migration:

- through the epidermis
- into the dermis which is well served with capillaries
- diffusion into the interstitial cement surround cells
- diffusion into the lipophilic secretion in sebaceous glands and hair follicles.

Cannabinoids are very lipophilic. Although the principal cannabinoids are not ionized and have a molecular mass of around 300 and a high milligram potency, the transdermal flux is low in human skin. Touitou, Fabin, Danny and Almog (1988) compared permeation kinetic parameters through human and rat skin *in vitro*. Rat skin was found to be about 13 times more permeable to ^{8}-THC than human skin. Autoradiographs of horizontal sections showed that 24 hours after application the drug was concentrated in the *stratum corneum*, in the upper dermis and around hair follicles, indicating that THC penetrates the skin through lipophilic pathways. These studies also examined the effect of oleic acid as a permeation enhancer, and in rats a serum level of approximately 50 ng/ml of THC and metabolites (measured as cross-reacting cannabinoids) was maintained for about 24 hours.

Compensation for the lower transdermal flux in human skin can be made to some extent by increasing the effective area of the patch. However, a patch with an area of 50 cm^2 with a drug reservoir concentration of 26.5 mg/g was calculated to provide a blood concentration of 12 ng/ml for THC. A number of later patents, many of which are probably speculative, are based on reservoir, drug in matrix types of composition. Penetration enhancers include DMSO, azone and oleic acid, which are well-tried substances to produce this effect.

One factor, which does not appear to be addressed in patch patents, is the practical point of disposal. In order to achieve linear diffusion of any agent into the skin it is necessary to have a steep concentration gradient. This means that the patch must contain relatively large amounts of cannabinoids to ensure linearity of transfer through the skin initially, and the kinetics of absorption are such that the used patch may contain as much as 90-95% of the original dose. This presents a real problem of how the spent dosage unit is to be disposed. A spent patch is likely to contain sufficient cannabinoid for several doses by the oral route, or by smoking.

The formulation of cannabinoids for topical application to the skin in the form of liposomes has been proposed by Touitou (1996). The essential components of the liposomes are a phospholipid, a lower aliphatic alcohol (C2-4), with aqueous propylene glycol as the solvent. It is claimed that the hydro/alcoholic/glycolic phospholipid system increases the permeation rate of a range of active compounds including cannabinoids through the skin. Transdermal application produces an approximately constant plasma level of cannabinoids, but it remains to be seen whether the pharmacokinetic profile produced by such devices is clinically effective.

Current research into cannabinoids has revealed that the body possesses an endocannabinoid system. The system, which is present in nearly all phyla from *Hydra* upwards is characterized by cannabinergic mediators such as anandamide and 2-arachidonyl glycerol (2-AG) that are derived from substances quite different chemically from the plant cannabinoids. The analogy between cannabinoids, vanilloids and opioids is striking. In each case there is a plant material, which appears to bind to the same receptors as endogenous ligands. Research into novel cannabinergic compounds has followed a similar pattern to that employed in the case of opioids. It has polarized into a search for synthetic agonists, antagonists, reverse agonists or partial agonists using the paradigms familiar to the pharmaceutical industry in the development of analgesics to replace morphine. It is approximately 200 years since Setürner isolated morphine from opium and about 30 years since the discovery of different types of opioid receptors and the endorphins. The search for novel cannabinergic compounds should not take as long. In the meantime there is an alternative route to novel cannabis based medicines. It depends on a renewed search for novelty in the clinical application of cannabis extracts containing known combinations of

cannabinoids. Not all of the actions of cannabis are based on receptors that are currently characterized, leaving open the possibility of further cannabinoid receptors. There are also other cannabinoids that have not been studied in the same detail as THC and CBD that may have clinical benefit.

In finding new cannabis-based medicines, an alternative to the pharmaceutical industry research approach is to build on the knowledge of receptor and non-receptor pharmacology and to explore the clinical benefit of these known compounds. It is probable that they will provide surprises in efficacy, but because man has already been exposed to them for thousands of years, they may not present so many problems in metabolism and toxicity.

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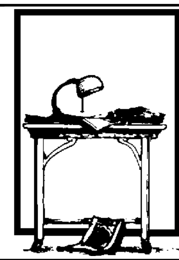
EDITORIAL



The *Journal of Cannabis Therapeutics: Studies in Endogenous, Herbal & Synthetic Cannabinoids* is pleased to present the first issue of its second volume. As we enter our second year, circumstances find the usual turmoil on cannabis political policy, while science marches on inexorably with new discoveries on its therapeutic effects, and an improved understanding of the role of endocannabinoids in human health and disease.

The current issue offers a good deal of new ground while reviewing recent historical foundations.

The first article by Russo et al. examines the benefits and side effects of cannabis in the Compassionate Investigational New Drug (IND) Program. The program was closed to new applicants in 1992. This study is the first of its kind to examine chronic cannabis usage in medical patients using a consistent source of medicine of known potency. The results are analyzed in the context of past chronic use studies in "recreational" consumers. We hope that this previously unavailable information will contribute useful data to the current clinical cannabis debate.

Ester Fride has become well known for her innovative work on the endocannabinoids, their patterns in growth and development and essential role in neonatal feeding behavior. We are now honored to present her latest offering on a putative new therapeutic possibility: applying cannabinoids to the complex pathophysiology of cystic fibrosis. I anticipate some would attempt to derogate such work as "speculative," but

this pejorative label is surely inappropriate when one considers the care, diligence and rigor that Dr. Fride has applied to the problem.

The new articles are rounded out with a submission by John McPartland, who has previously honored us with studies of anti-inflammatory mechanisms of the cannabinoids, and physiological effects of the "minor components" of cannabis. His revelatory new offering with partner Patty Pruitt moves us into the realm of the molecular biochemistry and genetics of cannabinoid receptors. Meticulous ontological examination assists us in understanding the evolutionary patterns of endocannabinoids and their role in bodily processes. Some may wonder how this could be construed as "therapeutic," but most often one needs to peruse the road map before setting forth on a grand journey. Such work tells us much about where we have been, and where we must go for a more thorough understanding of endocannabinoid function, and harnessing that power towards therapeutic advances.

The issue is rounded out with reviews of an eclectic selection of books: *Cannabis and Cannabinoids*, *Advances in Hemp Research*, *Waiting to Exhale*, *Hemp Diseases and Pests*, and *Mom's Marijuana*.

Ethan Russo, MD
Editor

Chronic Cannabis Use in the Compassionate Investigational New Drug Program: An Examination of Benefits and Adverse Effects of Legal Clinical Cannabis

Ethan Russo
Mary Lynn Mathre
Al Byrne
Robert Velin
Paul J. Bach
Juan Sanchez-Ramos
Kristin A. Kirlin

ABSTRACT. The Missoula Chronic Clinical Cannabis Use Study was proposed to investigate the therapeutic bepnefits and adverse effects of prolonged use of "medical marijuana" in a cohort of seriously ill patients. Use of cannabis was approved through the Compassionate Investigational New Drug (IND) program of the Food and Drug Administration (FDA). Cannabis is obtained from the National Institute on Drug

Ethan Russo, Robert Velin, and Paul J. Bach are affiliated with Montana Neurobehavioral Specialists, 900 North Orange Street, Missoula, MT 59802 USA (E-mail: erusso@blackfoot.net).

Mary Lynn Mathre and Al Byrne are affiliated with Patients Out of Time, 1472 Fish Pond Road, Howardsville, VA 24562 USA (E-mail: Patients@medicalcannabis.com).

Juan Sanchez-Ramos is affiliated with the Department of Neurology, University of South Florida, Tampa, USA.

Kristin A. Kirlin is affiliated with the Department of Psychology, University of Montana, Missoula, MT 59812.

Address correspondence to: Ethan Russo at the above address.

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Abuse (NIDA), and is utilized under the supervision of a study physician. The aim of this study is to examine the overall health status of 4 of the 7 surviving patients in the program. This project provides the first opportunity to scrutinize the long-term effects of cannabis on patients who have used a known dosage of a standardized, heat-sterilized quality-controlled supply of low-grade marijuana for 11 to 27 years.

Results demonstrate clinical effectiveness in these patients in treating glaucoma, chronic musculoskeletal pain, spasm and nausea, and spasticity of multiple sclerosis. All 4 patients are stable with respect to their chronic conditions, and are taking many fewer standard pharmaceuticals than previously.

Mild changes in pulmonary function were observed in 2 patients, while no functionally significant attributable sequelae were noted in any other physiological system examined in the study, which included: MRI scans of the brain, pulmonary function tests, chest X-ray, neuropsychological tests, hormone and immunological assays, electroencephalography, P300 testing, history, and neurological clinical examination.

These results would support the provision of clinical cannabis to a greater number of patients in need. We believe that cannabis can be a safe and effective medicine with various suggested improvements in the existing Compassionate IND program.

KEYWORDS. Cannabis, medical marijuana, hashish, investigational new drug, compassionate use, NIDA, FDA, herbal medicine, analgesia, spasticity, chronic pain, glaucoma, multiple sclerosis, epidemiology, history of medicine, drug policy

INTRODUCTION

The Missoula Chronic Clinical Cannabis Use Study was proposed to investigate the therapeutic benefits and adverse effects of prolonged use of "medical marijuana" in a cohort of seriously ill patients approved through the Compassionate Investigational New Drug (IND) program of the Food and Drug Administration (FDA) for legal use of cannabis obtained from the National Institute on Drug Abuse (NIDA), under the supervision of a study physician. The aim was to examine the overall health status of 8 surviving patients in the program. Four patients were able to take part, while three wished to remain anonymous, and one was

too ill to participate. Unfortunately, that person, Robert Randall, succumbed to his condition during the course of the study. Thus, 7 surviving patients in the USA remain in the Compassionate IND program.

Despite the obvious opportunity to generate data on the use of cannabis and its possible sequelae in these patients, neither NIDA, other branches of the National Institutes of Health, nor the FDA has published an analysis of information from this cohort. An examination of the contents of the National Library of Medicine Database (PubMed), and search engines of NIDA employing multiple combinations of key words failed to retrieve a single citation. The Missoula Chronic Cannabis Use Study thus provides a unique and important opportunity to scrutinize the long-term effects of cannabis on patients who have used a known dosage of standardized, heat-sterilized quality-controlled supply of low-grade medical marijuana for 11 to 27 years.

The results are compared to those of past chronic use studies in an effort to gain insight into the benefits and sequelae of this controversial agent in modern health care.

PREVIOUS CHRONIC CANNABIS USE STUDIES

The first systematic modern study of chronic cannabis usage was the *Indian Hemp Drugs Commission Report* at the end of the 19th century (Kaplan 1969; Indian Hemp Drugs Commission 1894). The British government chose not to outlaw cultivation and commerce of the herb after ascertaining that it had negligible adverse effects on health, even in chronic application.

Similar conclusions were obtained in the “LaGuardia Report” of 1944 (New York, NY), Mayor’s committee on marihuana (Wallace, and Cunningham 1944), which was the first to employ clinical and scientific methods of analysis.

Three important systematic epidemiological studies undertaken by research teams in the 1970’s exhaustively examined medical issues in chronic cannabis use, but remain obscure due to limited press runs and out-of-print status. The first of these was *Ganja in Jamaica: A Medical Anthropological Study of Chronic Marihuana Use* (Rubin and Comitas 1975). Therapeutic claims for cannabis were mentioned, but the focus of study was on “recreational use.” Sixty men were included in a hospital study of various clinical parameters if they had maintained a minimum intake of 3 spliffs a day for a minimum of 10 years. Jamaican ganja “spliffs” formed of unfertilized female flowering tops (sinsemilla) tend

to be much larger than an American “joint” of 500-1000 mg. The potency of the cannabis was analyzed with measures in 30 samples ranging from 0.7-10.3% THC, with an average of 2.8%.

In 1977, a detailed study was undertaken in Greece, titled *Hashish: Studies of Long-Term Use* (Stefanis, Dornbush, and Fink 1977). Once again 60 subjects smoking for more than 10 years were selected. Hashish potency was 4-5% THC and was generally mixed with tobacco. Alcoholics were excluded.

In 1980, *Cannabis in Costa Rica: A Study of Chronic Marihuana Use* was published (Carter 1980). Forty-one subjects smoking for 10 years or more were recruited. Although 10 or more cigarettes per day were smoked, the weight of material was only 2 g with an estimated THC range of 24-70 mg per day. Thirteen samples were assayed with a range of 1.27-3.72%, and average of 2.2% THC. Claims of benefit for cough, asthma, headache, hangovers, anorexia, impotence, depression and malaise were mentioned, but once more, the focus was on social use.

The current study is the first designed to examine clinical benefits and side effects of chronic clinical cannabis usage in which known amounts of quality-controlled material has been employed.

A BRIEF HISTORY OF THE COMPASSIONATE IND

Robert Randall was diagnosed with severe glaucoma at age 24 and was expected to become totally blind long before he turned 30. He soon began a fascinating medical odyssey that has been memorialized in his “personal reflection” co-authored by his wife, Alice O’Leary, titled *Marijuana Rx: The Patients’ Fight for Medicinal Pot* (Randall and O’Leary 1998), and other books (Randall 1991a; Randall 1991b). Until the day he died on June 2, 2001 at age 52 of complications of AIDS, Randall retained his vision, and remained a vocal advocate for the benefits of clinical cannabis.

His own journey commenced when he independently discovered that smoking a certain amount of cannabis eliminated the annoying visual haloes produced by his glaucoma. A subsequent arrest in August 1975 for cannabis cultivation led in turn to his dogged pursuit of the right to a legal means to supply his medicine of choice. He subsequently learned of medical support for his treatment (Hepler and Frank 1971). D. Pate has published two more recent reviews (Pate 1999; Pate 2001).

Through painstaking documentation and experimentation, Randall subsequently confirmed the inability of medical science to control his

intraocular pressure (IOP) by any legal pharmaceutical means. In contrast, smoked cannabis in large and frequent amounts was successful, where even pure THC was not. As Dr. Hepler observed in their experiments together (Randall and O'Leary 1998, p. 60), ". . . clearly, something other than THC or in addition to THC is helping to lower your pressures. . . . It seems that marijuana works very, very well."

After a great deal of bureaucratic wrangling, Randall obtained his first government supplied cannabis in November 1976, and the legal case against him was subsequently dismissed. The material he received from his study physician was cultivated in a 5-acre plot at the University of Mississippi, mostly from seeds of Mexican origin, and was rolled and packaged at the Research Triangle Institute in North Carolina under the supervision of the National Institute on Drug Abuse (NIDA).

Randall was encouraged to be thankful, but silent, about his treatment. Instead, he chose a different path (Randall and O'Leary 1998, p. 134), "Having won, why go mum? There were souls to save. Better to trust my fellow citizens and shout in to the darkness than rely on a devious Government dedicated to a fraudulent prohibition." He chose to make it his mission to seek approval of clinical cannabis for other patients. He developed protocols for glaucoma, multiple sclerosis, chronic pain, and AIDS that he shared with prospective medical marijuana candidates. Randall proved to be a tireless and persistent researcher, ferreting out hidden facts useful to his cause. Through the Freedom of Information Act (FOIA), he discovered in 1978 that the government's cost of cannabis cultivation and production was 90 cents per ounce (28 g), with 2/3 of this cost attributable to security measures. Thus, the actual cost of production approximated 1 cent per gram (US $0.01/g).

Supply and quality control issues arose frequently, and Randall and other patients experienced delays in receipt of shipments or substitution of weaker strains that required doubling of smoked intake.

The AIDS epidemic and its subsequent involvement in the medical marijuana issue suddenly provided an unlimited supply of available patients for the Compassionate IND program, and Randall assisted them as well. Some succumbed before their supply was approved, or shortly thereafter. By 1991, 34 patients were enrolled in the program according to Randall (Randall and O'Leary 1998), while other sources cite the number as only 15. Facing an onslaught of new applications, the Public Health Service (PHS) in the Bush administration closed the program to new patients in March 1992. A significant number had received medical approval but were never supplied. Randall sought to ascertain who signed the ultimate termination order through the FOIA, but was never

successful in this endeavor. At the time of this writing, 7 patients survive in the program.

METHODS

The identities of 6 of 8 of the original Compassionate IND program subjects were known to Patients Out of Time and were contacted in relation to participating in a study of the clinical parameters cited as concerns with chronic cannabis usage. Four subjects agreed to participate, and 3 traveled to Missoula, MT for testing at Montana Neurobehavioral Specialists, and Saint Patrick Hospital on May 3-4, 2001. One patient was tested to the extent possible in her local area due to physical limitations on travel (Patient Demographics: Table 1). Tests included the following (Tests Performed: Table 2): MRI scans of the brain, pulmonary function tests (spirometry), chest X-ray (P-A and lateral), neuropsychological test battery, hormone and immunological assays (CD4 counts), electroencephalography (EEG), P300 testing (a computerized EEG test of memory), and neurological history and clinical examination.

Past medical records were reviewed insofar as possible and the histories were supplemented with additional information. All patients signed informed consent documents, and the St. Patrick Hospital/Community Hospital Joint Investigational Review Board (IRB) reviewed the protocol.

RESULTS AND DISCUSSION

Case Histories and Test Data on Four Compassionate IND Program Patients

In the following section case histories, clinical examinations and objective test results are presented.

Patient A

Medical History: This almost 62-year-old female was born with congenital cataracts in Cali, Colombia and spent 13 years of her life there. There was a question of possible maternal exposure to malaria or quinine. Over time the patient required a series of 11 surgeries on the right eye and 3 on the left for the cataracts and had resulting problems with

TABLE 1. Chronic Cannabis IND Patient Demographics

Pt.	Age/Gender	Qualifying Condition	IND Approval/ Cannabis Usage	Daily Cannabis/ THC content	Current Status
A	62/F	Glaucoma	1988 25 years	8 grams/ 3.80%	Disabled Operator/ Singer/ Activist/ Vision stable
B	52/M	Nail-Patella Syndrome	1989 27 years	7 grams/ 3.75%	Disabled Laborer/ Factotum/ Ambulatory
C	48/M	Multiple Congenital Cartilaginous Exostoses	1982 26 years	9 grams/ 2.75%	Full time Stockbroker/ Disabled Sailor/ Ambulatory
D	45/F	Multiple Sclerosis	1991 11 years	9 grams/ 3.50%	Disabled clothier/ Visual impairment/ Ambulatory aids

glaucoma. Her last surgery was complicated by hemorrhaging, leading to immediate and complete loss of vision OD.

By 1976, the patient's intraocular pressure was out of control with all available drugs, many of which caused significant side effects. At that time she started eating and smoking cannabis to treat the condition. She underwent extensive testing in that regard, measuring pressures to titrate the dosage of cannabis. She initially had personal issues with the concept of smoking. Without cannabis her intraocular pressures may run into the 50's, while with it, values are in the teens to 20's. In 1988, she was arrested for cultivation of 6 cannabis plants. Her ophthalmologist noted (Randall and O'Leary 1998, p. 303), "it's quite clear-cut this is the only thing that will help her." At her trial, she stated in her own defense (Randall and O'Leary 1998, p. 305), "Marijuana saved my sight. I don't think the law has the right to demand blindness from a citizen." She was acquitted on the basis of "medical necessity," but her approval for the Compassionate IND program took 6 months. She had smoked cannabis on her own from black market sources for 12 years previously.

TABLE 2. Tests Performed: Chronic Cannabis IND Study

MRI scan of the brain
Pulmonary function tests (Spirometry)
Chest X-ray, P-A & lateral (Patients A-C)
Neuropsychological tests
Wechsler Adult Intelligence Scale–3rd Edition (WAIS-III)
Wechsler Memory Scale–3rd Edition (WMS-III)
California Verbal Learning Test (CVLT)
Halstead-Reitan Battery
Trail Making Test A & B
Grooved Peg Board
Finger Tapping and Category Subtests
Controlled Oral Word Association Test
Thurstone Word Fluency Test
Category Fluency Test (animal naming)
Wisconsin Card Sorting Test (WCST)
Conner's Continuous Performance Test–2nd Edition (CPT-II)
Beck Depression Inventory–2nd Edition (BDI-II).
Endocrine assays
FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone, progesterone
Immunological assays
CBC, CD4 count
Electroencephalography (EEG) (Patients A-C)
P300 testing (Patients A-C)
Neurological examination

At present, she also uses Timoptic® (timolol, beta-blocker) eye drops daily in the morning, but has concerns about resulting bronchoconstriction.

She normally uses cannabis 3-4 grams smoked and 3-4 grams orally per day. She feels that the amount that she receives legally from NIDA is insufficient for her medical needs. At times she accepts donations from cannabis buyers' clubs. She admits that the results of these outside cannabis samples on her intraocular pressure are unclear. She has had occasion to go to Amsterdam where intraocular pressures were measured in the teens simply employing cannabis available there. She has used Marinol® on an emergency basis, such as on traveling to Canada, in doses of up to 5-10 mg qid. She reports that it lowers intraocular pressure for one day, but within 3-5 days becomes useless for that purpose.

The patient has a history of cigarette smoking as well, 1-2 packs a day. She quit in 1997, but subsequently went on a "binge" of cigarette

smoking for 13 months, finally quitting on New Year's Day 2001. She feels that past pulmonary function has been normal.

She also notes lifelong insomnia that is alleviated by eating cannabis. Without such treatment, she feels she would sleep 4 hours, whereas with it she sleeps 6-7. She also feels that the drug produces antidepressant and antianxiety effects for her. She has a history of scoliosis, but notes no symptoms from this and feels that muscle relaxant effects of cannabis have made her quite limber.

The patient had a history of delirium associated with malaria as a child. She had some hardware in her foot from a 1980 surgery after a fall from platform shoes. She had a hysterectomy for fibroids. The patient was menopausal at age 48 and has had no hormone replacement treatment. There is no known history of specific meningitis, encephalitis, head trauma, seizures, diabetes, or thyroid problems. She is on no medicine save for cannabis and timolol eye drops. There are allergies to penicillin and tetracycline. She completed the equivalent of high school, and is right handed.

Family history is largely negative, although her 2 children had some cataract involvement.

Social history revealed that the patient has worked in the past as a switchboard operator. She is currently disabled due to legal blindness from her condition. She supports herself on Social Security Disability Income (SSDI). She has been an activist with respect to clinical cannabis. The patient drinks alcohol at a rate of about a bottle of wine a week. She had past heavy use of caffeine, but now drinks decaf only. The patient walks for exercise about an hour a day.

Medical Test Results: Objective: Weight: 132 lbs. OFC (Occipitofrontal Circumference): 55.5 cm. BP: 104/62. General: Very pleasant, cooperative 62-year-old female. Head: normocephalic without bruits. ENT: noteworthy as below. Neck: supple. Carotids: full. Cor: S1, S2 without murmur. On auscultation of the chest, there seemed to be a prolonged expiratory phase, but no wheezing. Mental Status: The patient was alert and fully oriented. Fund of knowledge, right-left orientation, praxis and naming skills were normal. She was unable to read a grade 6 paragraph with large type due to visual blurring. When it was read to her, memory of the contents was within normal limits. She performed serial 3's well. She remembered 3 objects for 5 minutes. On a word list task she named 15 animals in 30 seconds (normal 10-12). Speech and affect were normal.

Cranial Nerves: I: intact to coconut scent. II: acuity had recently been measured. There was no vision OD, 20/200 OS corrected. Visual

fields OS intact to confrontation. Optokinetic nystagmus (OKNs) was present in that eye in all fields. The patient is aphakic with an irregular eccentric pupil OS and clouding OD. The disk on the left appeared normal. There was prominent horizontal nystagmus resembling a congenital pattern. External extraocular movements were normal. Remaining cranial nerves V and VII-XII appeared intact in full.

Motor: The patient had normal tone and strength with no drift. Sensation was intact to fine touch, sharp/dull, vibration, position and graphesthesia. Romberg was negative. The patient performed finger-to-nose and heel-to-shin well. Rapid alternating movements of the hands were slightly clumsy and fine finger movements slightly deliberate. Gait including toe and heel were normal with tandem gait normal, but very carefully done. Reflexes were 2-3+, symmetric with downgoing toes.

The patient underwent a battery of tests. On pulmonary function tests (Table 3), a Functional Vital Capacity (FVC) was 103% predicted. Forced Expiratory Volume in 1 second (FEV_1) was 84% of predicted and the FEV_1/FVC ratio was 0.67. This was read as showing a mild obstructive defect based on the above ratio and flow volume curve morphology. No restrictive abnormality was noted. A CBC was wholly within normal limits (Table 4). Absolute lymphocyte count was 4.0, CD4 61.6% and absolute CD4 count 2465, all within normal limits. A full endocrine battery was performed (Table 5), including FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone, and progesterone, all within normal limits for age and gender.

TABLE 3. Pulmonary Function Tests

Patient/Parameter	A	B	C	D
FVC (% Predicted)	103	107	108	79
FEV_1 (% Predicted)	84	95	67	76
FEV_1/FVC	0.67	0.78	0.51	0.86
Interpretation	Mild obstructive Defect.	WNL. Slightly prolonged forced expiratory time.	Moderate obstructive defect.	No obstructive defect. Minor changes not excluded.

TABLE 4. Hematological/Immunological Parameters

Parameter/Pt.	A	B	C	D
CBC	WNL	Polycythemia	WNL	WNL
Lymphocytes, Absolute Count (K/µL)	4.0	3.4	1.8	2.3
CD4 percent	61.6	68.7	49.1	58
CD4 Absolute Count (/µL)	2465	2324	911	1325

TABLE 5. Endocrine Parameters

Parameter/Pt.	A	B	C	D
FSH (mIU/ml)	32.8	5.4	3.0	12.4
LH (mIU/ml)	20.6	3.8	4.1	16.2
Prolactin (ng/ml)	7.2	7.8	5.1	4.1
Estradiol (pg/ml)	8.0	10.0	10.0	212
Estrone (pg/ml)	15.0	20.0	22.0	146
Estrogen, total (pg/ml)	23.0	30.0	32.0	538
Testosterone (ng/dl)	7.0	505.0	296.0	34
Progesterone (ng/ml)	0.61	0.42	0.68	2.1
Interpretation	WNL for age and gender (menopausal).	WNL for age and gender.	WNL for age and gender.	WNL for age, gender and cycle (pre-menopausal).

An EEG was performed during wakefulness and early stages of sleep (read by EBR). A normal alpha background was identifiable at 12 hertz, along with a great deal of beta activity. Occasional left frontal phase reversing sharp waves were seen with rare episodes of slight slowing in the same area.

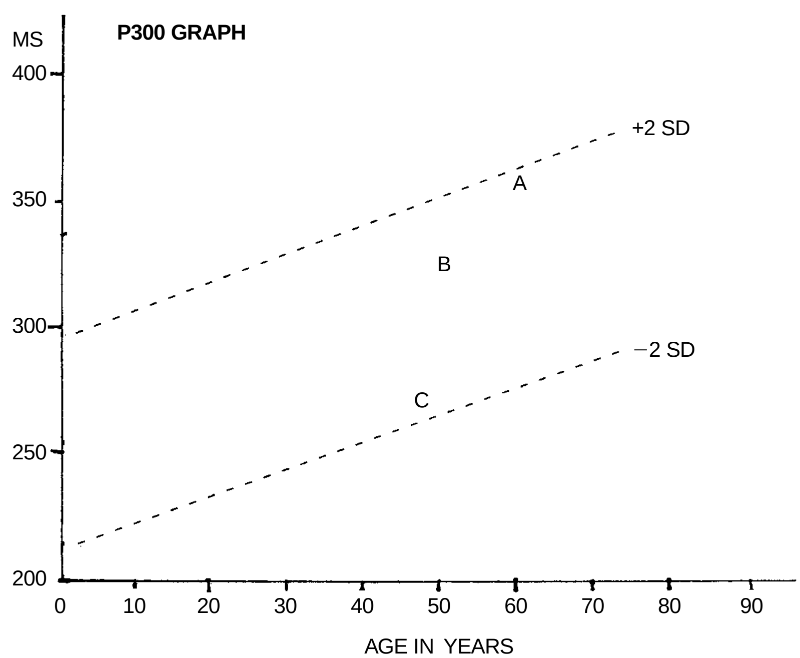
The patient had a P300 test performed with a latency of 355 milliseconds, within normal limits for a normed population in this laboratory (Figure 1).

The patient had an MRI brain study without contrast. This was read as showing a mild, symmetric, age consistent cerebral atrophy. A small focus of T2 hyperintensity and increased signal was noted on the FLAIR sequence in the mid-pons to the left of midline with no surrounding mass effect or edema. This was felt to be a nonspecific finding representing gliosis most likely from microvascular ischemic change. No corresponding signal abnormality was seen in the same area on a diffusion-weighted sequence.

A chest x-ray showed slight hyperinflation of the lung fields with no other findings.

Patient A was very pleasant and cooperative throughout the neuropsychological assessment and appeared to put forth very good effort. She did have very significant visual deficits and as a result, several instruments were dropped from the battery, including Grooved Peg Board,

FIGURE 1. P300 Latency Graph



Picture Arrangement, Symbol Search, and the Faces and Family Pictures Subtests from the Wechsler Memory Scale–3rd Edition (WMS-III). She was able to complete the Trail-Making Test A & B from the Halstead-Reitan Neuropsychological Battery, Spatial Span from the Wechsler Memory Scale–3rd Edition (WMS-III), and the Wechsler Adult Intelligence Scale–3rd Edition (WAIS-III)-Picture Completion, Digit Symbol, and Matrix Reasoning, but these were not used in interpretation secondary to the very probable interfering effects of her limited sight.

Review of the WAIS-III revealed a Verbal IQ in the upper end of the Average Range (VIQ = 108), and a Performance IQ in the Extremely Low Range, at only the 2nd percentile (PIQ = 69). This latter, however, is secondary to visual deficits as she had extremely low scores on the Digit Symbol and Picture Completion subtests. She obtained an age scaled score of 7 on Block Design; this performance was also adversely impacted by her visual defects to a mild degree.

Assessment of attention and concentration revealed that these abilities are mildly-to-moderately impaired relative to age-matched controls. She demonstrated an abnormally high number of omission errors on the Conner's Continuous Performance Test–2nd Edition (CPT-II) as well as significant variability of reaction time.

Formal assessment of learning and memory revealed that this subject's ability to acquire new verbal material on the WMS-III is within the Average Range relative to age-matched peers. Her Auditory Immediate Index score was in the average range as was her Auditory Delayed Index. She obtained index scores of 97 and 108 on these two indices, respectively. Recognition memory for auditory material was actually in the High Average range, the 75th percentile (Index Score = 110). In contrast she did much more poorly on visual measures secondary to very significant visual defects.

On the California Verbal Learning Test (CVLT), the subject generally performed within normal limits. Although initial learning trials were two standard deviations below expected limits, her ultimate acquisition at Trial 5 was one standard deviation above normative data sets. Short Delay Free Recall was perfectly normal and long delay recall was only one standard deviation below expected levels. This loss of recalled items from short delay to long delay free recall represented a loss that is approximately 1 standard deviation more than expected. Thus, she appeared to have mild difficulties with initial acquisition of very complex verbal material and also appeared to have minimal-to-mild difficulty retaining it in memory relative to age-matched peers.

Higher-level executive functions appear to be entirely normal in this patient. The Wisconsin Card Sorting Test (WCST) yielded a T-score of 63, while she obtained a T-score of 42 on the Category Test. Thus, she is still within the parameters seen in a normative data set of age and education-matched peers.

This subject's performance on the Thurstone Word Fluency Test was also entirely normal with a T-score of 51. Likewise, on the Controlled Oral Word Association Test, she obtained an overall score placing her at the 78th percentile. She produced 26 items on the Animal Naming Test over a 60-second period. This is within normal limits.

On the Beck Depression Inventory–2nd Edition, she obtained an overall score of 6, arguing against significant depressive symptoms.

In summary, Patient A appears to have mild-to-moderate difficulty with attention and concentration, and minimal-to-mild difficulty with the acquisition and storage of very complex new verbal material. General learning, however, as measured on the Wechsler Memory Scale–3rd Edition (WMS-III) appears to be within normal limits. Higher-level executive functions and verbal fluency abilities are well within normal limits.

Patient B

Medical History: This 50-year-old white male carries the diagnosis of the nail-patella syndrome, also known as hereditary osteo-onychodysplasia, a rare genetic disorder producing hypoplastic nails and kneecaps and renal insufficiency. Information was obtained from the patient, a published affidavit (Randall 1991b), and submitted medical records.

He first smoked cannabis in 1970, but did not become "high." Rather, he felt more relaxed, without his customary muscle spasms and pain. He first actually used clinical cannabis in a different manner. At the time he was mining, and he developed chemical burns in his hands. A Mexican lady gave him a tincture of cannabis flowering tops in grain alcohol to apply. This reduced his hand swelling and burning.

He has been smoking cannabis regularly for medical purposes since about 1974. During a medical crisis in 1985, he suffered a decrease in supply of available cannabis. His recollection is that all the various analgesics he received during this time were ineffective and produced of dangerous side effects including sedation and incapacity.

By 1988, he pursued regular usage of cannabis, about 1/8 of an ounce (3 1/2-4 g/d) a day when available. He initiated inquiries with the FDA

to obtain legal cannabis. Ultimately, with the assistance of Robert Randall, he received approval from the government in March 1990.

He related a history of deformities from birth including missing fingernails, loose finger joints, and small patellae. He was frequently ill as a child, and at age 10, suffered a progression from conjunctivitis to varicella, strep throat and rheumatic fever. He was hospitalized for 6 months, and required another 3 months of bed rest. Subsequently, he underwent four right knee surgeries, reconstructions and rotations, including 3 arthroscopies. He had had a right wrist graft with non-fusion. He had had right elbow surgery and had a "nicked" ulnar nerve. In the late 1960's he developed both hepatitis A and B with prolonged hospitalizations. Despite this, he pursued heavy manual labor in mining, construction, auto bodywork and aircraft repair. He lost all his teeth by age 21. In 1972 he dislocated his knee and had 3 subsequent surgeries. In 1976 he had a wrist fracture with subsequent surgery and later fusion. In 1978 he was hospitalized after a nail wound in his foot failed to heal. In 1983, he injured his back in a fall. Pain continued.

After a 1985 chiropractic session, he became acutely ill with severe back pain. He was given narcotics, and suffered renal failure. He was transferred to a university center. Lithotripsy sessions were followed by transurethral procedures in attempts to clear his nephrolithiasis. Eventually an open procedure was performed for perinephric abscess, but the flank wound failed to heal over the course of a year. Ultimately, it was determined that he was suffering a tubercular nephritis. He took triple therapy with isoniazid (INH), rifampin and pyridoxine regularly for 18 months. Eventually, a massive debridement was necessary, before the flank wound eventually healed. His prolonged convalescence forced him to close his business.

On September 3, 1987, he complained of persistent flank pain and low back discomfort increasing over the preceding 2 years treated with multiple modalities, including TENS unit. He also was using an abdominal binder. Pain radiated to the buttocks and posterior thighs. X-rays of the lumbar spine showed spondylolisthesis grade 1 in the lumbar area with no significant motion of flexion extension views.

On April 8, 1988, the patient was seen for right knee pain after a twisting injury and fall. An effusion developed. X-rays showed a micropatella consistent with nail-patella syndrome, but no evidence of fracture. He was treated conservatively. In October, 1988, chest x-ray showed a diffuse nodular infiltrate unchanged since September 1985.

By June 7, 1989, the patient was in a wheelchair, but was able to ambulate with a cane. Previous x-rays showed bilateral iliac spurs. His

chart notes included an FDA consent form in relation to the patient's use of cannabis (Figure 2). On subsequent visits, he had been approved for the Compassionate IND program, and was smoking 10 cannabis cigarettes a day.

On April 1, 1991, some cough was noted attributed to cigarettes. As a baseline, very severe pain was noted in the extremities, but this was reduced to slight to moderate on subsequent visits. By April 17, 1991, the patient was on no medicines except for cannabis. By January 18, 1993, he was said to have only slight to moderate problems with a cane for support. There were some abdominal spasms.

On the May 14, 1996 visit, he was smoking 10 cannabis cigarettes a day. He used occasional aspirin for increased pain. He had resumed smoking 1/2 to 1 pack of cigarettes a day. Examination was fairly unremarkable save for orthopedic deformities. He was able to walk on his toes and heels. The patient was given 2 more packages of 300 marijuana cigarettes.

On July 16, 1996, the patient was seen for disability examination. It was noted the patient had suffered for many years from lack of strength, mobility and range of motion, and persistent episodes of nausea and muscle spasms. The note indicated, "the marijuana helps the patient function better in the sense that he has increased flexibility, increased strength and range of motion. He has less nausea and less muscle spasm." He needed to shift into different positions at home to get comfortable and could do a sit down type job for an hour or two at most before experiencing spasms, pain and nausea. He had limited backward flexion, and limited right hand strength. He was unable to kneel. He could walk 50 feet before needing to rest, used a cane and sometimes a wheelchair for longer distances. It was felt he could not be a traveling salesman, and any prospective job would require frequent rests. Overall, he was assessed as having a significant functional impairment due to nail-patella syndrome, and was judged unemployable in the short or long term, with little rehabilitation potential.

A May 9, 1997 letter indicates, "continues to smoke about 8-10 marijuana cigarettes per day and still continues to benefit from that medication. He has less pain, less spasms, he is able to ambulate better. His nausea is improved, he is able to sleep better. He is making some slow deterioration of this disease process." It goes on to say, "I personally do feel that [Patient B] continues to benefit from marijuana and hope that we can continue providing this unfortunate man with marijuana medication."

FIGURE 2. Informed Consent Document, Patient B

FD 1571 Atachment 10(b)

PATIENT CONSENT FORM

I, ______________________, understand that this study will evaluate marijuana's use in the treatment of symptoms of chronic pain and muscle spasticity caused by severe spinal cord injuries. As a patient who suffers from intense pain and uncontrollable spasticity, I am interested in marijuana's potential medical uses and I volunteer to participate in this study of marijuana's effect on my symptoms.

I realize that in addition to marijuana's possible benefits in controlling pain and reducing spasticity, the drug may also cause various side effects including, but not limited to, alterations in consciousness and mood, anxiety, euphoria, drowsiness, depression, disorientation, paranoia, confusion, rapid pulse, pounding of the heart, dizziness, fainting, bloodshot eyes and dryness of the mouth. Although not validated by clinical studies, I understand some researchers believe marijuana may cause damage to the lungs and brain, changes in hormone levels, personality changes and/or reduce the body's ability to fight infection. However, I also understand marijuana, at the dosages I will receive, has been well tolerated by other patients who smoke marijuana to reduce intraocular pressures, control nausea and vomiting and ease spasticity. Due to marijuana's reported side effects I agree not to operate a car or other motor vehicle if I become intoxicated while smoking marijuana.

During this study I will be under the care of my doctor. I understand that if I experience any adverse effects while smoking marijuana I should report these effects to my physician. If I leave my doctor's care I understand my access to marijuana will be terminated unless another physician responsible for my care receives FDA approval to provide me with marijuana. I also understand that if for any reason I decide to leave this program, my doctor will notify the FDA of my decision and marijuana will be unavailable to me for this purpose.

Signed ______________________ Date __________, 1989

Witness Date __________, 1989

Witness Date __________, 1989

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On May 10, 2000, a letter to FDA noted the patient continued to do well on the therapy, smoking 8-10 cigarettes per day without other medication. He continued to function well using a cane and occasionally a wheelchair when bothered by spasms and nausea.

At present, he utilizes about 7 grams a day or 1/4 ounce of NIDA material that is 3.75% THC, and was processed in April 1999. The patient cleans the cannabis to a minimal degree first, estimating a loss of about 25% of material. He indicates that he has been short on his supply 3 times in 10 years, generally for 1-2 weeks, secondary to lack of supply or paperwork problems. When this occurs he suffers more nausea and muscle spasms and is less active as a consequence. He was never allowed to try Marinol®, and points out that he could not afford it in any event.

The patient reports continued problems with pain in the back, hips and legs, also in the upper extremities, right greater than left. When he undergoes spasms the pain rises to a 10 on a 10-point scale and is associated with projectile emesis. His baseline level of pain is 6-7/10. He notes that this pain was never helped by prescription medicines. Morphine sulfate produced a minimal decrement in pain for up to two hours, but caused inebriation. By the third day of application it would become totally ineffective. Without cannabis he feels that he would need very high doses of narcotics. He previously had dependency issues and took heroin for 2 years in the mid-1960's. Eventually he had become allergic to most pharmaceutical preparations, or had side effects of nausea. The latter continues, particularly in static positions, which without cannabis treatment he rates as a 10/10. In 1985, he was without cannabis for some 30 days and lost 57 pounds when his supply ran out at the same time that he had TB nephritis.

In relation to the spasms, these can occur anywhere in his body. He feels the medicine eliminates them or substantially reduces nocturnal manifestations. Without it he would be "running" at night.

He has no history of diabetes, thyroid problems, meningitis, encephalitis, or head trauma. He may have had seizures associated with fever. The patient has taken rare antibiotics for staph infections of the skin. He feels that he has had lots of reactions to synthetic chemicals of various types, which he considers quite serious. The patient left school at age 14 originally, but attained a GED and had some junior college experience. He is left-handed.

Family history is noteworthy for nail-patella syndrome in mother, niece, two sisters, nephew and daughter. One sister died of the disease

at age 44. He has two unaffected children. His affected daughter does not receive legal cannabis. His father died of TB and tumors at age 40.

Social History: He currently smoked cigarettes about 1/2 pack a day, but as high as a pack a day in the past. The patient drinks beer about 1 a month, with little alcohol use in 10 years. The patient last worked full-time in 1985, and part-time in 1990. He is on SSDI, but does volunteer and activist work. The patient is able to walk very little due to pain, but bikes when he can a short distance (about 4 miles every other day). The patient sleeps from 10 p.m. to 6 a.m., but this is disrupted due to pain or nausea.

Medical Test Results: Weight: 173 lbs. Height: 69 inches (BMI: 25.6). OFC: 60 cm. BP: 122/80. General: Very pleasant, cooperative 50 YOM who appears somewhat wizened. Head: normocephalic without bruits. ENT was noteworthy for edentulous state. Neck: supple. Carotids: full, without bruit. Cor: S1, S2 without murmur. The patient has a large indentation scar in the right flank. Palpation to the spine was unremarkable. Chest auscultation revealed a prolonged expiratory phase without wheezing. Abdominal examination was unremarkable. He had dysplastic nails.

Mental Status: The patient was alert and fully oriented. Fund of knowledge, right-left orientation, praxis and naming skills were normal. He read a grade 6 paragraph well with good recall. Serial 3's were well done. Signature was normal. He remembered 2 of 3 objects after 5 minutes with hesitation, failed the third with hint, but got it with choice of 3. He had a hoarse voice. He named 11 animals in 30 seconds (normal). Affect was normal. Cranial Nerves: I: intact. II: acuity was measured as 20/25 OD, 20/50 OS uncorrected. Fields and OKNs were normal. Fundi were benign. Pupils equally reactive with full EOMs and no nystagmus. Remaining cranial nerves V and VII-XII were unremarkable. On motor examination, the patient had hypotonicity, but decreased bulk. The patient lacked full elbow extension on the right. His strength was generally 4+ secondary to limitations and pain. There was no arm drift. Sensation was intact to fine touch, vibration, position and graphesthesia, but there was some slight vibratory loss in the feet. Romberg was negative. The patient performed finger-to-nose well. Heel-to-shin required partial assist of the hands. Rapid alternating movements of the hands were very slow on the right secondary to mechanical problems. Fine finger movements were normal. The patient had a stiff, bent gait, but toe gait appeared more normal. On heel gait he favored the left leg. Tandem gait was difficult due to back pain and he

wavered some. I was unable to ascertain reflexes at the biceps on the right, but responses elsewhere were 1-2+ with downgoing toes.

The patient underwent the prescribed battery of tests. Pulmonary function tests revealed an FVC of 107% of predicted, FEV_1 of 95% of predicted, and FEV_1/FVC of 0.75. This was interpreted as within normal limits, but with a slightly prolonged forced expiratory time (Table 3). A complete blood count showed some mild polycythemia, probably due to tobacco smoking. An absolute lymphocyte count was 3.4 with CD4 count 68.7% and absolute count of 2324 (Table 4). The patient had a full endocrine battery. Measurement of FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone and progesterone were wholly within normal limits for age and gender (Table 5). An EEG was performed during wakefulness and was within normal limits, but did demonstrate some low voltage fast activity in the beta range, with no focal or epileptiform activity. The patient had a P300 response with a latency of 338 milliseconds, within normal limits for the laboratory (Figure 1). An MRI of the brain without contrast was read as normal. A PA and lateral chest was read as normal.

Patient B was friendly and cooperative and appeared to put forth very good effort on neuropsychological testing. On the WAIS-III, he obtained Verbal and Performance IQ Scores in the Average Range (VIQ = 105 and PIQ = 92). In terms of overall intellectual functioning, he obtained an overall score placing him at the 50th percentile (Full Scale IQ = 100). Assessment of attention and concentration with the CPT-II revealed that these abilities tended toward mildly-to-moderately impaired relative to the normative data set. He made an abnormally high number of omission errors and also demonstrated substantial variability in his reaction time. He also became more variable as time progressed over this 14-minute measure.

On the WMS-III, he obtained Auditory Immediate and Auditory Delayed Index scores of 89 and 86, placing him in the low average range. His Auditory Recognition Delayed Index was in the average range with an index score of 90. Visual Immediate and Visual Delayed abilities were also in the low average range with index scores of 88 on both. Overall, these performances are within normal limits, albeit it in the low average range.

On the CVLT, this patient's initial acquisition of items after the first trial was one standard deviation below expected levels, and his recall after five learning trials was two standard deviations below. Short Delay Free Recall and Long Delay Free Recall were essentially at the same level. Thus, his acquisition of very complex verbal material does appear

at least mildly impaired. Interestingly, he does not lose this information from memory after a delay.

Assessment of higher level executive functions yields an overall performance on the WCST at a mildly impaired level relative to age and education matched peers, with a T-score of 38. His overall performance on the Category Test was in the borderline range with a T-score of 40. He also had difficulty following new complex sequences with a T-score of 40 on the Trails A Subtest and a T-score of 32 (mildly-to-moderately impaired) on the Trails B component.

Simple motor testing reveals that Tapping Speed was within normal limits, but he had difficulty with fine motor coordination on the Groove Pegboard Test with his dominant left hand. He obtained a T-score of 36 on this particular measure with his left hand, a T-score of 42 with his right hand.

On the Thurstone Word Fluency Test, he obtained a T-score of 54 and a T-score of 40.2 on the Controlled Oral Word Association Test. Animal naming was within normal limits with a total score of 22.

In summary, Patient B does appear to have a mild-to-moderate impairment of attention and concentration, and his ability to acquire new, complex detailed verbal material also appears to be mildly-to-moderately impaired. There is quite some variability in this regard, however, with performances on the Wechsler Memory Scale–3rd Edition (WMS-III) being generally within normal limits, and his California Verbal Learning Test (CVLT) performance falling approximately 2 standard deviations below expected levels. He had difficulty on motor tasks. His performances may have been adversely affected by peripheral pain as he complained of such during the assessment process. His overall score of 0 on the Beck Depression Inventory (BDI) argues against significant depressive symptoms.

Patient C

Medical History: This 48-year-old male carries a diagnosis of multiple congenital cartilaginous exostoses, an autosomal dominant disorder. History was obtained from the patient, a published affidavit (Randall 1991b), and submitted progress notes dating from December 5, 1996.

He recalls few medical problems until age 10, when he threw a baseball and his arm became paralyzed for a few hours. Radiographs revealed what was interpreted as an old fracture that had healed with jagged bone fragments. Multiple referrals ensued, and ultimately 250 bony tumors were found throughout his body. He was diagnosed as hav-

ing multiple congenital cartilaginous exostoses. Each was capable of growth, massive tissue disruption, pain, and malignant transformation. By age 17, he underwent multiple surgical procedures on the left leg, and right wrist. By age 12, constant pain and frequent hemorrhages severely limited his gait along with other basic functions. He required a home tutor by grade 7. By age 14, he required ongoing narcotics for analgesia, escalating to Dilaudid® (hydromorphone), and Sopor® (methaqualone, now Schedule I in USA) for sleep. He reports resultant fatigue, ennui, and disorientation as side effects.

At age 20, he developed a large bone spur on the right ankle, which recurred dramatically after one surgery. Amputation was recommended, but refused. At age 22, a fist-sized tumor was removed from the pelvis. A medical odyssey ensued, which failed to identify better therapies and he required massive doses of hydromorphone, methaqualone, and muscle relaxants.

He described himself as a conservative young man who was against drugs, but in college acquiesced to try marijuana. He enjoyed chess, but was normally able to sit for only 5-10 minutes without pain. One day, he smoked cannabis and an hour into a chess match he remained pain-free. After discussion with his doctor, he experimented by smoking it regularly for 6 months. He noted a marked enhancement of his analgesia, and a reduction on his dependence on hydromorphone (taken intravenously for some time), Demerol® (meperidine), and hypnotics. Cannabis analgesia exceeded that of any prescription drugs.

He began to investigate possible legal avenues to obtain cannabis, and met Robert Randall in 1978. By 1979, he was spending $3000 annually on therapeutic cannabis through the black market, an unsustainable burden. A Byzantine bureaucratic process ensued over several years, with final FDA approval of his IND application in November 1982. Weekly monitoring sessions including needle electromyography (EMG) were deemed necessary to assess the effects of treatment in his protocol.

Subsequently, he described numerous instances of delayed shipments of cannabis, or exhaustion of supplies of higher potency product. Substitution of 1% THC cannabis required a doubling of dosage to 20 cannabis joints a day.

He was once arrested in Florida despite documentation, handcuffed and jailed overnight, sustaining an ankle hemorrhage in the process. Only 4 of 7 confiscated joints were ultimately returned. Beyond this, he describes cannabis as much safer than prescribed medicine, and free of

serious adverse effects except chest pain with prolonged usage of inferior product.

In 1992, Patient C had occasion to try Marinol® during a stockholders meeting in Canada due to his legal proscription from traveling with cannabis. Although he had no side effects on a dose of 10 mg, it was without any benefits, and left his muscles very tight and painful.

Detailed progress notes from the last several years were obtained and will be summarized. December 5, 1996, the patient was using 10-20 mg of baclofen and 10-15 cannabis cigarettes a day. Assessment was of multiple congenital cartilaginous exostoses with hepatitis C, and GE reflux. He was prescribed diazepam 5 mg for spasm. An EKG was read as showing normal sinus rhythm. February 28, 1996, the patient had pulmonary functions with FVC 112% of predicted, FEV_1 of 79% of predicted, read as indicating mild obstruction.

January 24, 1997, he had episodic spasm with pain affecting both arms and legs. It was noted at the time that the patient had a malunion of the right radius. He was down to 2-3 cannabis cigarettes a day, as he had received no supply from NIDA since September 1996, due to logistical problems in seeing his study physician. A transfer of providers was recommended.

September 4, 1997, he remained on baclofen 10 mg p.m., 5 mg a.m. and Prilosec® (omeprazole) for epigastric discomfort that had been going on for 7 years, and cannabis 12 cigarettes a day. September 9, 1997, the patient had a chest x-ray with no findings. September 9, 1997, the patient had laboratory tests done, including a CBC, non-reactive hepatitis A and B tests, and normal thyroid functions. Glucose was low at 24, potassium high at 5.4, SGOT 79 with other parameters negative. September 17, 1997, the patient was said to be doing well smoking 10-12 cannabis cigarettes a day with dramatic decreases in frequency and intensity of flexor spasms. He was also taking baclofen. It was noted that with strong spasms the patient would bruise his skin and sometimes even bleed. His weight was constant, appetite normal. Neurological exam was fairly unremarkable. He was asked to slowly decrease the baclofen to 2.5 mg bid.

May 13, 1998, the patient was said to be doing quite well. In the interim, a liver biopsy demonstrated minimal changes secondary to hepatitis C. Chest x-rays were said to show no changes. The prior December the patient had twisted his left knee with a lot of swelling, and an MRI revealed a minor crack in the tibial head. Pain was under good control with 12 cannabis cigarettes a day with only occasional muscle spasms. Exam was unremarkable. He was said to be doing quite well off of the

baclofen and was asked to continue 12 cigarettes of cannabis a day. May 26, 1999, the patient related no difficulty breathing. Weight was constant. There was dull pain in the ankles and some sharp shooting also in the knees. There was minor weakness in the right hand with no other deficits. The remainder of the exam was normal. The patient was felt to be doing well and advised to continue 12 cannabis cigarettes a day. October 6, 1999, the patient was seen in follow up, was on omeprazole, Vitamin C, and cannabis. The patient had some congestion and mildly productive cough. He was felt to have acute bronchitis and was given cough syrup. January 5, 2000, the patient had pulmonary functions done with an FVC 118% of predicted, FEV_1 82% of predicted. This was felt to indicate borderline obstruction. January 13, 2000, glucose was 126, BUN 26, SGOT 71 with other parameters normal, including CBC. Hepatitis C antibody was reactive with other titers negative. Thyroid functions were normal. An SGPT was 181.

May 4, 2000, the patient was occasionally playing softball and had no complaints of shortness of breath. Again there was mild weakness of the hand with other muscles normal. It was felt that the patient was doing well without aches, pains or spasms on his cannabis.

November 21, 2000, the patient had noticed some increased discomfort following a motor vehicle accident the prior month wherein he was rear-ended and had neck pain. Subsequently, he noted persistent pain in the right thigh. An x-ray was negative. He tried physical therapy, heat and electrical stimulation. He noted more muscle tension with weather change. No neurological changes were observed.

December 28, 2000, the patient was on his omeprazole and cannabis. January 6, 2001, SGOT was 50, SGPT 94 with normal CBC and PSA. A cholesterol total was 221 with LDL 136.

At the time he was examined in Missoula, he noted constant baseline pain of 9-10 on a 10-point scale without cannabis. At rest, with cannabis this fell to a 4/10. He was smoking 9 grams a day of 2.7% THC NIDA cannabis, or 11 ounces every 25 days. At times he has had to cut back due to an inadequate supply. He would sometimes have to use street cannabis at a cost $110 per quarter ounce (circa $16/g) of an estimated 4-5% THC content. Interestingly, although he found the flavor was an improvement over the government supply, he noted little difference in analgesic effect except, but perhaps greater relaxation effect. Interestingly, even with extensive cannabis use there are only two times he thinks that he ever may have been "high." One time he left his coat somewhere in freezing weather, which is extremely uncharacteristic, and the other he had been without cannabis for a long time and briefly

felt euphoric while smoking. However, once he advanced to a second joint, this feeling was gone.

The patient has the most problems with the left arm where pain is a 7-8/10 when there are flare-ups despite medicine. This decreases after he takes rofecoxib (Vioxx®) for a week. He experiences pain in both knees, but usually minimal (1-2/10) with his cannabis. He may periodically pull a muscle or hemorrhage, especially in the ribs. He has occasional problems in the wrist.

The patient's sleep remains disrupted rarely attaining 6 hours total. Typically, he is up every 45 to 60 minutes with stiffness and needs to have pillows to position himself. He once got 8 hours of sleep with methaqualone (now illegal in USA), waking only twice.

He feels that his hepatitis C is asymptomatic and was probably due to a transfusion in his teens. Although he did use hydromorphone intravenously for a long period of time, he feels that he pursued a scrupulous aseptic technique. Besides surgeries noted above, he has dental caps due to bruxism, and tonsillectomy. He has had past hypertension, which he feels was work related. There is no history of diabetes, thyroid problems, meningitis, encephalitis, head trauma or seizures. He uses only omeprazole 30 mg a day regularly in addition to his cannabis. He is allergic to barbiturates. The patient had 3 semesters of college. He is primarily right-handed, somewhat ambidextrous.

Family history is negative for other known involvement, but his father was adopted. His mother has migraine.

Social History: The patient works full time as a stockbroker. He is also a very decorated disabled sailor. He plays softball once a week. He may use a stationary bike about 10 minutes at a time, but this is subject to weather effects. He does not smoke tobacco. The patient drinks about 1.75 liters of Jack Daniels whiskey every 10-14 days, which helps him sleep. He does not drink coffee.

Medical Test Results: Weight: 153 lbs. Height: 5′ 4 1/2″. General: Very pleasant, cooperative 48-year-old white male who is somewhat obese (BMI: 25.5). Head: normocephalic without bruits. ENT: unremarkable. Neck: supple. Carotids: full, without bruits. Cor: S1, S2 without murmur. The patient had very slight gynecomastia. He has prominent exostoses of the left shoulder, left wrist, right shoulder, and right calf. Auscultation of the chest revealed a prolonged expiratory phase without wheezing. Abdominal palpation was negative.

Mental Status: The patient was alert and fully oriented. He knew the president and had normal right-left orientation, praxis and naming skills. He read a grade 6 paragraph well with good recall. Serial 3's were

done very rapidly. He remembered 3 objects for 5 minutes. He named 15 animals in 30 seconds, which is well above the average of 10-12. Speech and affect were normal.

Cranial Nerves: I: intact. II: fields and OKNs were normal. Fundi were benign. Pupils were equally reactive with full EOMs and no nystagmus. Remaining cranial nerves V and VII-XII were unremarkable. On motor exam, the patient had some limitation due to pain, but seemed to have good strength throughout except for 4+/5 foot dorsiflexion on the right. There was no drift. Sensation was intact to fine touch, vibration, position and graphesthesia, but there was decrease in sharp/dull discrimination at the top of the right foot secondary to post-operative changes. Romberg was negative. Finger-to-nose and rapid alternating movements of the hands were normal. Heel-to-shin was incomplete on the right, better on the left. Fine finger movements were minimally decreased. On gait testing the patient slightly favored the right leg at the ankle. Toe gait looked better. Heel gait was barely possible due to pain on the right side. Tandem gait was minimally hesitant. Reflexes were 1+, symmetric with downgoing toes.

Medical Test Results: On pulmonary function tests, an FVC was 108% of predicted and FEV_1 67% of predicted. A FEV_1/FVC was 0.51 felt to be indicative of a moderate obstructive defect based on the latter ratio and flow volume curve morphology. No restrictive abnormality was noted (Table 3).

A CBC was wholly within normal limits. An absolute lymphocyte count was 1.8 with CD4 49.1% and CD4 absolute count of 911 (Table 4). An endocrine battery, including FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone and progesterone, was wholly within normal limits for age and gender (Table 5).

An EEG was performed during wakefulness and early stages of sleep, which was within broad normal limits. There was a good bit of low voltage fast activity in the beta range. No focal nor epileptiform activity was appreciated. A P300 showed a latency of 262 milliseconds felt to be within normal limits for the lab (Figure 1).

An MRI was performed without contrast. There was felt to be no definite abnormality of an acute nature. There were some minor changes in the right parietal area suggestive of a mild degree of gliosis with associated dilated perivascular spaces of doubtful significance. There was a small area of abnormal signal in the right parotid gland overlying the right masseter muscle felt to be probably benign.

A P-A and lateral chest x-ray were performed. This was read as showing a pulmonary nodule in the left upper lobe with minimal airway

changes. One examiner (EBR) reviewed those films and felt that the lesion was actually located in a rib. As a result, the patient underwent a CT scan of the chest after returning home. This showed no evidence of mass, lymphadenopathy, or pulmonary nodules. A small amount of pleural calcification was noted. An exostosis was noted in the right anterior 3rd rib, accounting for the false-positive chest x-ray.

On neuropsychological testing, Patient C was pleasant, cooperative, and appeared to put forth very good effort. His attention was noted to be quite poor at times and many instructions had to be repeated.

On the WAIS-III, he obtained Verbal and Performance IQ Scores in the Average Range with a Verbal IQ of 103 and a Performance IQ of 104. In terms of overall intellectual functioning, he is currently performing at a level equal to or above 58 percent of the general population (Full Scale IQ = 103).

Assessment of attention and concentration with the CPT-II revealed that immediate attentional abilities were within normal limits. His ability to concentrate, however, did appear mildly impaired, as he tended to lose efficiency with the passage of time. Thus, vigilance appeared to be mildly decreased relative to a normative data set.

On the WMS-III, Patient C obtained an Auditory Immediate Index in the Average Range at the 70th percentile. His Auditory Immediate Index was 108. Auditory Delayed Index was also 108, placing him in the Average Range, and his Auditory Recognition Delayed Index was 115, placing him in the High Average Range. The Visual Immediate Index was 115 with a Visual Delayed Index of 122, performances in the High Average and Superior Ranges, respectively.

On the CVLT, this patient's initial acquisition on Trial One was two standard deviations below expected levels and his acquisition of only ten items by Trial 5 was one standard deviation below expected levels. Short Delay Free Recall was also one standard deviation below expected levels but he performed within normal limits if provided cues. His ultimate free recall after a 20-minute delay was also one standard deviation below expected levels. There was not a substantial loss of information between Long Delay and Short Delay Free Recall trials. Thus, his ability to acquire very complex and detailed new verbal material does appear minimally-to-mildly decreased relative to age matched peers, well below his ability to acquire new thematically organized verbal material, which was in the above average range. Memory, however, appears normal.

Assessment of higher level executive functions yielded a T-score of 45 on the WCST and a T-score of 44 on the Category Test from the

Halstead-Reitan Neuropsychological Battery. His ability to follow new complex sequences was entirely within normal limits as indicated by T-scores of 52 and 62 on Trail Making Test A and B, respectively.

Simple motor speed measured by Finger Tapping was within normal limits, bilaterally, as was fine motor coordination measured by the Grooved Pegboard Test.

His performance on the Thurstone Word Fluency Test yielded a T-score of 56, which is entirely within normal limits relative to age and education-matched peers. Likewise, his overall performance on the Controlled Oral Word Association Test yielded a T-score of 52.52, and Animal Naming Fluency also was within normal limits. His overall score on the Beck Depression Inventory-2nd Edition (BDI-II) was 0.

Overall, Patient C appears to have mild difficulty sustaining attention and also minimal-to-mild difficulty with the acquisition of very new, complex verbal material. Overall, however, he appears to be functioning quite well.

Patient D

Medical History: This 45-year-old female carries a diagnosis of multiple sclerosis (MS). The patient was interviewed by telephone (EBR) in lieu of the possibility of contemporaneous examination. The patient feels her first problem may have occurred at age 18 when her vision sequentially went completely black for two months with slow improvement over a subsequent four months. A possible attribution to oral contraception was hypothesized. She was subsequently evaluated at a quartenary referral center and diagnosed as having retro-bulbar neuritis. She was prescribed nicotinic acid. On re-evaluation in 1983, no active disease was noted. On May 29, 1986, best corrected vision was 20/30 OD, 20/25 OS. By May 19, 1988, values fell to 20/200 OD, and 20/70 OS. The patient was formally diagnosed as having MS April 1 of that year with associated bilateral optic neuropathy. She had had symptoms for perhaps 6 months with blurring in both eyes and leg spasms that interfered with walking. The patient had never used cannabis recreationally, and began it only because of her symptoms.

She has been followed in her local area by a psychiatrist and neurologist. Extensive, well-documented notes commencing December 20, 1989 were provided, and will be summarized. When first seen on that date the patient was married for the second time. It was noted that she had been diagnosed with MS about a year and a half previously and had been on diazepam from time-to-time. She was taking 10 mg tid to cope

with stress. She had previously tried trazodone and buspirone, had become paralyzed with her MS, and was consequently very frightened of these medicines. On examination she was felt to be quite anxious and was provisionally diagnosed as having a dysthymic disorder.

On March 20, 1990, she seemed to be suffering from more depression, although she managed to smile. She described difficulty with self-esteem and hopelessness. She had only been taking diazepam intermittently and was rather prescribed Prozac® (fluoxetine) 20 mg and Xanax® (alprazolam) 0.25 mg up to 3 times a day. She was felt to have recurrent major depression. On subsequent visits the patient had slight adjustments of medicine and was feeling better by May 2, 1990. By August 6, 1990, the patient was having greater difficulties with insomnia. She was given trazodone 50 mg at bedtime on a trial basis. August 24, 1990, the patient was only sleeping until 4 a.m., which was about 2 hours better than without medicine. This was increased to 75 mg.

The patient had heard about some studies of using cannabis in MS as a relaxing agent. She indicated that she had tried this with a good relaxation response. There was a discussion of possible effects on the lungs, and her expected diminished life expectancy because of MS. She was given a prescription for Marinol® (dronabinol, synthetic THC) 10 mg to be tried q 4 hours prn to see if this would help with relaxation and nausea. When seen September 5, 1990, she had found that the Marinol® had reduced the nausea considerably and had even helped her vision. She continued on fluoxetine.

September 27, 1990, the patient was not sleeping well, possibly due to fluoxetine, and was given a benzodiazepine. October 17, 1990, the patient was seen in follow up and was on Xanax® (alprazolam). It was noted that she had improvement with Marinol®, but the patient noted she actually had a better response to smoked cannabis. They began to look into obtaining a legal supply.

December 3, 1990, the patient reported increased depression and was increased to 40 mg a day of fluoxetine. December 5, 1990, the patient had recurrent depression even on the fluoxetine 2 a day and low dose alprazolam. Apparently, her doctor had received notification that he could no longer prescribe Marinol® "off label" unless a Schedule I permit for cannabis was being pursued. December 19, 1990, the patient reported nausea, for which some of her remaining Marinol® had helped. January 16, 1991, the patient complained of spasticity spells and episodes of nausea. She had run out of Marinol® and had no cannabis supply. She indicated she had tried other medications without success and was resistant to try others due to side effects.

February 20, 1991, the patient had purchased illicit cannabis in the interim. Apri, 16, 1991, the patient continued on fluoxetine 20 mg bid. More jerkiness was noted with increased spasticity. She had not smoked cannabis before coming in. It was felt that she would need 6 cannabis cigarettes a day to reduce symptoms. May 10, 1991, she was taking alprazolam about every 2 weeks. She was continuing to have some spasms. She continued to try cannabis illicitly, but had not yet obtained it legally. June 14, 1991, she had lost her driver's license due to visual problems associated with MS. During this interval there were more marital issues. July 2, 1991, it was indicated the patient was legally blind and there were no possible corrective measures. Plans were in place to obtain legal cannabis for spasticity and nervous problems. It was noted that cannabis seemed to be very effective for her clinically. August 7, 1991, the patient was still without a supply and complained of her legs jerking at night, and increased difficulty walking. The patient requested Marinol®, but this could not be prescribed. She was given baclofen 5 mg tid to try.

August 30, 1991, she received her fist shipment of NIDA cannabis, seven months after approval of the Compassionate IND. The patient was advised that she should confine her use to government cannabis. She was having problems with her gait, able to walk only with a cane. There were continued vision problems. She complained of left sided weakness. The patient smoked a cannabis cigarette in front of the doctor, which led to her feeling better. It was suggested she try 3 cannabis cigarettes a day. September 3, 1991, the patient reported that the government supply of cannabis did not have the "punch" that street bought material had. Her dose was increased to 5 joints a day. It was indicated that her spasticity responded positively to the dose increase. September 11, 1991, the patient was on 5 NIDA cigarettes a day. This was helping her spasticity. She was unclear as to whether her vision was helped. September 20, 1991, it was felt that 7 cigarettes a day would be necessary. The patient reported increased muscular activity, uncontrollable at times. October 2, 1991, the patient had run out and was noticeably more spastic on examination. Her dose was increased to 10 a day. October 9, 1991, the patient was on 10 cannabis cigarettes a day of the strongest available dosage, which seemed to help her spasticity. She was walking without a cane. It was not felt that her depression was improved. November 4, 1991, she had been out of her supply for 10 days. Spasticity increased and she complained of pain in the left leg. Increased tone was noted throughout the body. December 5, 1991, apparently a supply came in of lower potency cannabis. December 19, 1991, it was felt she

had continued improvement of her spasticity with better gait. February 14, 1992, she was using 1 can of cannabis a month, equal to 300 cigarettes. The patient reported she had not been falling. March 13, 1992, she continued the cannabis at the same rate, plus 40 mg of fluoxetine and no alprazolam. The patient reported she was able to walk, swim better, and do all of her ADL's much easier than she could prior to the cannabis. There was no observable gait disturbance on exam.

April 14, 1992, it was felt that she got a lot of relief from her medicine and that it "probably offers her greater efficacy in her spasticity, also, than Valium would." May 19, 1992, the patient continued to be stable with no exacerbations of her MS and the spasticity under good control. There were concerns about periodontal disease from her dentist. It was thought she might do better with less smoking of a higher potency supply. The patient was also smoking cigarettes and was subsequently advised to avoid tobacco. By July 17, 1992 she continued to respond to cannabis. September 18, 1992, reflexes were equal and not hyperactive. November 16, 1992, there was an increase of depression slowly and insidiously. December 9, 1992, the patient had been off of her treatment for a week and was very shaky. Smoking a joint in front of her doctor caused her to become calm, less shaky and better able to walk. January 19, 1993, she got her first cans of the stronger cannabis, which the patient felt more effective after smoking one joint. March 22, 1993, she was smoking 6-7 a day. She seemed better after smoking one in the office. April 22, 1993, the patient was smoking 10 cigarettes a day. Smoking produced a decrease in spasticity as observed. There were no adverse effects that were noted in the office. May 24, 1993, the patient was tried on lorazepam. June 24, 1993, the patient was upset with financial issues and was placed on Mellaril® (thioridazine). July 22, 1993, when she was examined, no tremor or spasticity was noted. Again cannabis was smoked with no adverse effects noted. August 30, 1993, the patient requested a decrease in her fluoxetine. She felt that spasticity and depression were both helped by the cannabis. September 29, 1993, the patient reported that on a lower fluoxetine dose she was getting tearful. Reflexes were not hyperactive. November 2, 1993, the patient had some paresthesias on the left side, but was maintaining good motor control. December 28, 1993, she was tried on bupropion. January 4, 1994, problems had been noted on bupropion and it was not as effective. She was tried on sertraline. She reported that the cannabis helped her to not think about her MS. She was having fewer spasticity problems.

February 4, 1994, when the patient smoked cannabis in the office, she seemed to be a little more talkative and relax significantly with less

spasticity and no adverse effects. February 28, 1994, again significant relief from spasticity was noted upon smoking. March 30, 1994, the patient had some numbness and tingling in the limbs. The patient reported the new material was stronger and had a better effect. May 9, 1994, some increase in emotional lability was noted. The patient was taken off of sertraline and put on Effexor® (venlafaxine). May 25, 1994, she was unable to tolerate the latter and was started back on fluoxetine. August 29, 1994, she continued on fluoxetine and cannabis. Smoking a joint calmed her and limited tremor. September 28, 1994, it was indicated in relation to cannabis "it seems to have a positive effect on her mental status overall." October 31, 1994, the patient was felt to be without signs of depression. She actually lowered her dose on a higher potency material. February 1, 1995, the patient was on diazepam again. February 14, 1995, she was increasingly shaky and tearful. March 29, 1995, she was hardly able to walk due to an exacerbation. May 2, 1995, she still needed support. At the same time the patient was having marital difficulties. August 4, 1995, the patient reported she could see much better with the cannabis. By September 6, 1995, she was walking quite well and was no longer on diazepam, merely the fluoxetine and cannabis. October 4, 1995, she continued to walk well with no problems.

January 17, 1996, an MRI revealed multiple bilateral periventricular and diffuse white matter changes in the cerebrum and cerebellum, but seemingly fewer than on a April 4, 1995 study.

April 19, 1996, the patient had been out of cannabis for a week and was experiencing more spasticity and ambulation difficulties. She was more depressed. May 17, 1996, the patient had been tried on a stimulant. July 10, 1996, the patient reported that cannabis was the only thing that had helped her with her symptoms over the course of her illness.

By September 25, 1996, the patient had been without medicine for a month and had to buy it on the street. She had lost weight and her condition had reportedly decompensated to some degree. The patient reported a 10-pound weight loss. November 13, 1996, the patient was having difficulty sleeping, but did not wish to take trazodone. November 27, 1996, the patient had fallen and had a brief loss of consciousness. December 5, 1996, she had had an episode of spasticity that was the worse she had ever had, starting in the neck and going down her back. January 8, 1997, cannabis came in after a summer drought since September 25. An emergency supply was requested. January 22, 1997, the patient remained concerned about lack of cannabis supply. February 5, 1997, she continued with this concern. February 19, 1997, there was discussion of difficulty the patient had experienced with the authorities in an airport.

April 2, 1997, it was felt the patient continued to get a great deal of relief from smoking 10 joints a day without any adverse effects. July 2, 1997, the patient was observed to become more loquacious and interactive after dosing.

Janary 29, 1998, the patient was not complaining of spasticity, seeming to have considerable relief with cannabis. Her fluoxetine was lowered to 20 mg a day. March 24, 1998, it was felt that she had a very slow progression of her MS helped by her consumption of cannabis. September 22, 1998, the patient said that the medicine took away her fear of the disease and when she would get a pain she would be able to smoke and take it away.

October 27, 1998, she apparently had been out of her supply for 6 weeks, but had gotten by smoking only 4 cigarettes a day instead of the usual 10. January 24, 1998, the patient was doing relatively well and was walking with a cane. December 22, 1998, she was having increasing problems. January 26, 1999, the patient indicated that medicine helped her maintain her weight. March 24, 1999, it was observed, "I think her spasticity is being helped with the cannabis." April 23, 1999, she continued to get good relief with 10 cigarettes a day. June 24, 1999, the patient reported some increasing difficulty with walking in the heat and hot weather. July 20, 1999, she was said to have no tremor or spasticity. September 1, 1999, she was having some exacerbation and difficulty walking and limping because her right leg was not working as well. October 20, 1999, the patient reported the only bad side effect would be when she smoked too much she would tend to go to sleep. She discussed alternative treatments for multiple sclerosis with her doctor and they agreed not to pursue them. November 19, 1999, the patient was walking on a wide base felt to be the result of a mild exacerbation. November 24, 1999 neurological examination confirmed greater ataxia. Methylphenidate was prescribed.

December 1, 1999, an MRI of the brain was said to reveal multiple focal white matter changes in bilateral cerebral areas especially in the basal ganglia and in the cerebellar peduncle, compatible with MS.

January 12, 2000, the patient was tried on Ritalin® (methylphenidate). She was switched to Remeron® (mirtazapine) from fluoxetine. February 22, 2000, the patient reported that her eyes were improved. March 9, 2000, visual acuity was 20/200 OD and 20/80 OS. April 6, 2000, it was felt that she had no declines in function from cannabis use.

June 27, 2000, her cannabis had been late coming in and she had cut from 10 to 6 or 7 cigarettes a day, feeling that that had hurt her physically and that she was not walking as well. January 31, 2001, the patient

was a little bit down and labile, but by February 28, 2001, she was not depressed or hyper. April 11, 2001, she was having some trouble walking due to a flare of symptoms, which had been present for a month, but she noted no changes in vision.

When the patient was interviewed by EBR (June 2001), she reported that her vision was currently clear with cannabis. She was able to ambulate without aids, but has to stop after a block or less due to weakness. She swims a few days a week. She feels that there is no nystagmus in her vision and no diplopia. She characterizes her MS as mildly progressive.

The patient indicated that she received the cannabis legally in 1991 and continues to smoke 10 cigarettes a day. She currently receives material of 3.5% THC content that was processed April 1999. Her study physician requests the highest potency material available, which has recently varied between 2.9-3.7% THC. When she uses outside cannabis of higher potency, she feels that she gets twice the relaxation. There is no chronic cough or other difficulties. The patient feels that Marinol® at 10 mg was too strong. She used it for 6 months before the cannabis. Customarily she splits each of her supplied cigarettes in two, and manicures it slightly. When she is not on cannabis she has had no withdrawal symptoms, but has had increase in movement problems.

The patient has had a tubal ligation. She continues to menstruate on a regular monthly basis. Her main problems have been depression and some degree of anxiety. I asked about other diagnoses and she replied that she had “10 personalities and they are all feeling fine!” She denied history of diabetes, thyroid problems, meningitis, encephalitis, head trauma or seizures. The patient remains on fluoxetine 40 mg a day. She is allergic to penicillin. The patient had 1 year of college. She is right handed.

Family history is noteworthy for father having narcolepsy and a sister who is bipolar.

Social History: She had one child by choice. The patient is a retired clothier, and is unable to work at this time. She is currently smoking 1/2 pack of cigarettes a day, previously 1 pack a day, and has smoked since age 20. The patient does not drink at all, has not for 5 years, nor has she ever had a problem with alcohol. She does not drink coffee. She customarily sleeps 8 hours.

Medical Test Results: The patient is 5 feet tall and 97 pounds (BMI: 19). On pulmonary function tests, an FVC was 79% of predicted, and FEV_1 76% of predicted. The FEV_1/FVC was 86 (Table 3). There was felt to be no obstruction based on this ratio or analysis of the F/V curve

morphology. Early small airway disease and borderline restrictive disease (e.g., due to MS) were not excluded.

A CBC was wholly within normal limits. An absolute lymphocyte count was 2.3 with CD4 of 58% and CD4 absolute count of 1325 (Table 4). An endocrine battery was performed, with values of FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone and progesterone, all within normal limits for age an gender (pre-menopausal female) (Table 5).

Neuropsychological tests were performed in her home on June 17, 2001. Some confusion was noted throughout the evaluation and significant fatigue over the course of the day was also apparent. She did not have significant difficulty with instructions, however, and effort and cooperation were sufficient to obtain what is believed to be valid data. As a result of significant visual deficits, many visually based tests were omitted and interpretations from those requiring significant visual input were provided in a very cautious manner. For example, this patient required a magnifying glass in order to accomplish the Picture Completion and Trails subtests that very likely had a significant negative impact on her overall performance.

On the WAIS-III, the patient obtained a Verbal IQ of 93. A Performance IQ was not calculated secondary to significant visual deficits that interfered with assessment in this realm. On the WMS-III, the patient performed, on verbal measures, in the Low Average Range. Immediate auditory memory was at the 18th percentile, with an auditory delayed index in the Average Range. Her ability to acquire non-thematically-organized verbal material was in the mildly impaired range relative to age-matched peers, but her retention was actually very good. Also, she did very well on a test measuring her ability to acquire verbal paired associates with a learning slope actually in the above average range, and excellent retention. Her ability to acquire more detailed and non-thematically-organized verbal information was moderately-to-severely impaired relative to age-matched peers. Overall performances on the CVLT ranged from two to five standard deviations below expected levels. Numerous intrusions during both free and cued recall were noted at levels above and beyond what is generally seen in the normative population. She made eight false-positive errors on recognition testing, which are also an abnormally high number of errors.

Concentration was noted to be markedly impaired in this patient, following the mildly-to-moderately impaired range overall. Assessment of Executive Functions reveals that abstract concept formation and logical analysis abilities were significantly reduced, falling in the moderately impaired range overall. The patient was also noted to be quite perse-

verative, having difficulty shifting cognitive strategies. In slight contrast, flexibility of thought as measured by the Similarities Subtest from the WAIS-III, was within normal limits. Verbal Fluency was within normal limits relative to age and education-matched peers.

In summary, this patient appears to have decrements in concentration, low average learning, and memory efficiency for new thematic material and verbal paired associates. Her ability to acquire more detailed and non-thematically-organized verbal information is at least moderately impaired. Memory functions, however, appear to be normal in the sense that once she acquires information, she seems to hold it quite effectively. Higher level executive functions are reduced at a moderate level despite a very remarkable psychiatric history. Responses to the BDI-II were well within normal limits.

Patient D thus demonstrates numerous neurocognitive impairments. The general pattern is not particularly uncommon in the context of multiple sclerosis and significant psychiatric dysfunction. This profile, when combined with the others from the data set do not provide any consistent pattern that one could reasonably ascribe to the therapeutic use of cannabis.

Review of Neuropsychological and Cognitive Data

The scientific study of the effects of chronic cannabis on cognition has remained problematical since such concerns were first raised. Despite intensive effort in this regard, little in the way of "hard findings" or consistent results has emerged. A complete review of alleged problems is beyond the scope of this article, but a few citations are meritorious.

In the Jamaican studies (Rubin and Comitas 1975), 19 neuropsychological tests were administered to chronic cannabis users and controls with no major significant differences between groups. In fact, ganja smokers scored the highest on Wechsler Adult Intelligence Scale (WAIS) Digit Span performance ($p < 0.05$). The authors concluded (p. 119), "in a wide variety of human abilities, there is no evidence that long-term use of cannabis is related to chronic impairment."

In Greece (Kokkevi and Dornbush 1977), no differences were noted between hashish users and age and socio-economically matched controls in total or Performance IQ (PIQ) scores on the WAIS. Controls performed better on three subtests: Comprehension ($p < 0.01$), Similarities ($p < 0.005$), and Digit Symbol Substitution ($p < 0.05$). Control Verbal IQ (VIQ) surpassed that of users ($p < 0.05$). However, these results must be viewed in light of the fact that normal population studies in

Greece revealed PIQ:VIQ differences of 7 points. Thus, the authors concluded (p. 46), “These observations do not provide evidence of deterioration of mental abilities in the hashish users.”

In Costa Rica, an extensive battery of neuropsychological measures showed no pathological changes (Carter 1980). It was observed (p. 188), “we failed to uncover significant differences between user and nonuser groups–even in those subjects who had consumed cannabis for over eighteen years.”

Subsequently follow-up studies were performed on some of this cohort, and certain significant differences were claimed, including learning of word lists and selective and divided attention tasks (Fletcher et al. 1996). However, a detailed critical analysis of those results in *Marijuana Myths, Marijuana Facts* (Zimmer and Morgan 1997) seems to deflate any such claim.

Lyketsos et al. (1999) studied effects of cannabis on cognition in 1318 adults over a period of 12 years. No differences were noted in the degree of decline between heavy, light, and non-users of cannabis on the Mini-Mental State Examination (MMSE). Critics have indicated that the latter represents too crude a tool to measure the issue properly.

In a series of studies in the 1990’s summarized in a book, *Cannabis and Cognitive Functioning* (Solowij 1998), Nadia Solowij studied subjects employing cannabis at least twice a week on average for a period of 3 years. After a review of data, the author stated (p. 227), “the weight of the evidence suggests that the long-term use of cannabis does not result in any severe or grossly debilitating impairment of cognitive function.” She did note more subtle difficulties in attention parameters including distraction, loose associations and intrusion errors in memory tasks. In a recent review of cognitive effects of cannabis (Solowij and Grenyer 2001), it was observed (p. 275), “the long term risks for most users are not severe and their effects are relatively subtle. . . .”

Results from the current study seem to indicate similar findings. As part of a Comprehensive Neuropsychological Evaluation, all subjects were administered a battery of instruments including the WAIS-III, the WMS-III, the CVLT, the Trail Making Test A and B, Grooved Peg Board, Finger Tapping, and Category Test, the Controlled Oral Word Association Test, the Thurstone Word Fluency Test, a Category Fluency Test (Animal Naming), the WCST, the CPT-II, and the Beck Depression Inventory–2nd Edition (BDI-II).

Comparing Patients A-D, it appears that all four do have at least mild difficulty with attention and concentration, and verbal acquisition of varying complex new verbal material (as measured on the CVLT),

which is at least minimally impaired. Importantly, however, higher-level executive functions generally appear to be within normal limits in two of the subjects.

Difficulties in attention and concentration as well as new complex verbal learning may be directly related, and must be understood in the context of not only these subjects' chronic cannabis use, but also their underlying chronic diseases and clinical syndromes, with attendant fatigue and preoccupation. Interestingly, depressive symptoms are not currently noted at a clinical level in any of the subjects despite their chronic medical conditions or long-term cannabis use. None displayed evidence of social withdrawal or apathy characteristic of the alleged "amotivational syndrome." Rather, all were animated, engaging in conversation and demonstrating an active involvement with their ongoing care and the current research.

Overall, once more, no significant attributable neuropsychological sequelae are noted due to chronic cannabis usage.

Review of Neuroimaging

In 1971, it was reported that "consistent cannabis smoking" of 3-11 years in ten patients produced evidence for cerebral atrophy employing air encephalography (Campbell et al. 1971), an excruciatingly painful and long abandoned technique. Subsequent study by Kuehnle et al. (1977) employing CT scans on 19 men with long durations of heavy cannabis usage failed to show any changes in the ventricles or subarachnoid spaces. They criticized the prior study for lacking controls on antecedent head trauma or other causes of neurological damage. In the same issue of the *Journal of the American Medical Association*, Co et al. (1977) studied an additional 12 heavy cannabis smokers who displayed no CT abnormalities.

In 1983, an additional 12 subjects who smoked more than 1 g of cannabis daily for 10 years were studied by CT scans of the brain, and only one with concomitant history of alcoholism showed any abnormalities compared to controls (Hannerz and Hindmarsh 1983).

Most recently, Block et al. (2000) employed automated imaging analysis with MRI to examine 18 young heavy users of cannabis. No abnormalities were ascertained. The authors stated (p. 495), "frequent marijuana use does not produce clinically apparent MRI abnormalities or detectable global or regional changes in brain tissue volumes of gray or white matter, or both combined." It was recently noted (Solowij and Grenyer 2001, p. 270), "There is no evidence from human studies of

any structural brain damage following prolonged exposure to cannabinoids."

Despite this additional documentation, the claim of brain damage and cerebral atrophy remains a popular myth in prohibitionist rhetoric.

Current MRI studies on Patients A-C with a General Electric Sigma LX MR 1.5 Tesla magnet system reveal no clear abnormalities. Patient A had age-compatible atrophy, and Patient C had minor tissue changes of a non-specific nature, commonly seen in middle-aged populations. Patient D has previously demonstrated MRI brain lesions consistent with MS, with possible improvement observed during the period of clinical cannabis usage.

Review of Neurophysiology Tests

In discussing the issue of cannabis and cerebral effects, Homer Reed observed (Reed 1975, pp. 122-123), "The association between many of the EEG measures used to indicate CNS changes and the clinical condition of the patient is approximately zero." That not withstanding, various researchers have advanced numerous claims of pertinent EEG changes due to cannabis. Cohen (1976) noted differences in computerized EEG measures of delta band power and theta band phase angle (lead/lag) relationship. No mention was made of the alleged significance of these tests, or of the results of standard EEG.

All the Jamaican subjects had EEG examinations (Rubin and Comitas 1975). As previously noted in other studies, 9 of 30 cannabis smokers had significant low voltage fast activity in the beta range. Although this finding may indicate sedative effects of medication, it is often ascribed to a normal variant. Three of the 30 were said to have unequivocal focal abnormalities, but 4 of 30 controls had similar findings, and another had diffuse abnormalities. Overall, no significant differences were noted between ganja smokers and controls.

Similarly, in Greece (Panayiotopoulos et al. 1977), 8.8% of 46 hashish smokers had abnormal EEGs, while 15% of 40 normal controls were so characterized. The authors stated (p. 62), "We failed to find either an abnormality or an particular EEG change in the resting EEG records of chronic hashish users. . . ."

Current results, performed on a 21-channel Nicolet Voyageur digital EEG system and read by EBR, confirm the presence of low voltage fast activity in Patients A-C, and intermittent sharp waves and rare subtle slowing in the left frontal area in Patient A. Age appropriate atrophy was seen in the same patient on MRI, but she has no history of seizures

or CNS insults. There are no corresponding abnormalities on neurological examination. Similar abnormalities are identified on EEGs of 6% of patients, whereas there is only a 0.5% prevalence of seizure disorders in the general population. In essence, no EEG pathology of an attributable nature seems apparent in the study group on the basis of cannabis usage.

With respect to P300 responses, a type of electrophysiological event related potential, even greater caution is necessary. This parameter is offered as an electrophysiological measure of memory, inasmuch as prolongation of its latency occurs with age. The test was popular in the 1980's as an objective test for dementia. Amplitude differences have also been noted in different clinical conditions, but were termed (Spehlmann 1985, p. 370), "of uncertain diagnostic importance because of the great normal variability of the P300 amplitude." Overall, these issues and significant incidence of false positives and false negatives have largely relegated use of this technique to the sidelines as a clinical tool.

Solowij (1998) studied the P300 in chronic cannabis users vs. controls, and noted results felt to be indicative of (p. 150), "inefficient processing of information and impaired selective attention." These consisted of reduced processing negativity to relevant attended stimuli, inappropriately large processing negativity to a source of complex irrelevant stimuli, and reduced P300 amplitude to attended target stimuli to that of controls.

In contrast, Patrick et al. (1995) examined the P300 in psychologically normal chronic cannabis users and controlled the data for age. Results showed no amplitude differences.

More recent studies have shown significant reductions in P300 amplitude in schizophrenia (Martin-Loeches et al. 2001), but also in cigarette smokers (Anokhin et al. 2000), with notable effects according to motivational instructions (Carrillo-de-la-Pena and Cadaveira 2000), and even diurnal variations (Higuchi et al. 2000).

Our study employed a Nicolet Viking 3P 4-channel system with a P300 oddball paradigm. Patients A-C displayed P300 latencies that were well within norms for age-matched controls (Figure 1).

Review of Pulmonary Issues

Pulmonary concerns remain paramount in relation to chronic cannabis smoking. Excellent recent reviews are available (Zimmer and Morgan 1997; Tashkin 2001; Tashkin 2001). In brief, cannabis smoking produces an increase in cough and bronchitis symptoms, but to a lesser degree than in tobacco smokers (Sherrill et al. 1991). Daily cannabis

smokers seek medical care for smoking-associated health concerns at a slightly higher rate than non-smokers (Polen et al. 1993). In a large epidemiological study, cannabis use was associated with little statistical association on total mortality in women, and non-AIDS mortality in men (Sidney et al. 1997).

One of the primary associated risks of tobacco smoking is the development of emphysema and lesser declines in bronchial function over time. A careful longitudinal study of chronic smokers has demonstrated a longitudinal decline in the FEV_1 in tobacco smokers, but not heavy cannabis smokers (Tashkin et al. 1997).

Some association of cannabis smoking has been observed to head and neck cancers (Zhang et al. 1999), and pre-cancerous cytological changes have been noted in the lungs in bronchoscopy studies (Fligiel et al. 1988), but to date, no cases of pulmonary carcinoma have been noted in cannabis-only smokers.

In examining the data from chronic cannabis use studies, in Jamaica, a slight downward trend not attaining statistical significance was noted on forced vital capacity (FVC) values (Rubin and Comitas 1975). A similar downward trend was observed on FEV_1 without statistical significance. No differences between cannabis smokers, occasional smokers and non-smokers were observed on FEV_1/FVC ratios. Results of all tests may have been affected by concomitant tobacco usage.

The Greek studies did not closely examine pulmonary function, and although an increase in bronchitis symptoms was noted in hashish smokers over abstainers, the former group also smoked more tobacco. Differences were not statistically significant in any event (Boulougouris, Antypas, and Panayiotopoulos 1977).

In the Costa Rican studies, no spirometry measures were significantly different between cannabis users and non-users. However, statistical trends were, in fact, positive with respect to cannabis usage. Cannabis smokers displayed larger indices of small-airway patency. The authors suggested that in concomitant smoking of tobacco, cannabis seemed to counteract the expected effects of tobacco on small airways. The author stated (Carter 1980, p. 171), "at least it cannot be said of the users that they have suffered an additive of [sic-"or"] synergistic decrement in pulmonary function over that attributable to tobacco alone."

In our Patients A-C, no ultimate chest radiographic changes of significance were noted, despite a false-positive reading of pulmonary nodule in Patient C. It is of particular note that he has had a previous bronchoscopy procedure with no reported cytological changes.

Observed pulmonary function values in this cohort reveal no clear trends except a slight downward trend in FEV_1 and FEV_1/FVC ratios, and perhaps an increase in FVC (Patients A-C) (Table 3). Concomitant tobacco smoking (Patients A, B, and D) complicates analysis. It is particularly interesting that Patient B, a current concomitant smoker of tobacco displayed the best spirometry values, while those in Patient C, a never-smoker of tobacco were the worst. His underlying connective tissue disease may have played an active role in this finding. His use of the lowest grade cannabis and highest amount per day are the more likely explanation.

Significant questions remain as to the role of low-grade NIDA cannabis as a contributor to the above findings, which will subsequently discussed.

Review of Hematological Studies

No effects on complete blood counts or hemoglobin were observed in the LaGuardia Commission report (New York, NY). Mayor's committee on marihuana (Wallace and Cunningham 1944). In the Jamaican studies, slight increases were observed in hematocrit and hemoglobin readings in cannabis smokers over controls, but results were affected by concomitant tobacco use (Rubin and Comitas 1975). No hematological data was obtained from the Greek studies.

In Costa Rica, a downward trend was observed in hematocrit readings of cannabis smokers, but this was not statistically noteworthy (Carter 1980).

In our studies (Table 4), Patient B, a concomitant tobacco smoker, displayed a mild degree of polycythemia and slightly elevated WBC. No other hematological changes of any type were evident in the other three patients.

Review of Immunological Parameters

Immune system damage remains an area of contention with respect to cannabis usage (Zimmer and Morgan 1997), but one in which there is considerably more heat than light. A closer examination of the available literature may allay concern.

In the chronic use studies in Jamaica, no decrement was observed in cannabis smokers vs. controls in either lymphocyte or neutrophils counts (Rubin and Comitas 1975). Neither were significant changes noted in the data in Costa Rica (Carter 1980).

In the 94-Day Cannabis Study, initial acute low values were observed in T cell counts, but these returned to normal over the course of the testing (Cohen 1976).

A closer examination of the pertinent literature raises concerns on theoretical levels to a greater degree than practical ones. Excellent reviews are available (Klein, Friedman, and Specter 1998; Hollister 1992; Cabral 2001; Cabral 2001).

Early reports of inhibition of cell mediated immunity in cannabis smokers (Nahas et al. 1974) were refuted by later studies in which no impairment of lymphocytic response to phytohemagglutinin in hashish smokers was observed (Kaklamani et al. 1978).

A seminal review of the topic was undertaken by Hollister (1992), who stated (p. 159), "evidence of altered immune functions is derived mainly from in vitro tests or ex vivo experiments, which employed doses of cannabinoids far in excess of those that prevail during social use of marijuana." More recently, Klein, Friedman and Specter (1998) have similarly noted (p. 102), "Although cannabinoids modulate immune cell function, it is also clear that these cells are relatively resistant to the drugs in than many effects appear to be relatively small and totally reversible, occur at concentration higher than needed to induce psychoactivity (> 10 µM or > 5 mg/kg), and occur following treatment with nonpsychoactive cannabinoid analogues." They added (p. 102), "The public health risk of smoking marijuana in terms of increased susceptibility to infections, especially opportunistic infections, is still unclear." Finally, despite concerns raised by THC effects on immunity in animals and *in vitro*, Cabral and Dove Pettit (1998) admitted (p. 116), "Definitive data which directly link marijuana use to increased susceptibility to infection in humans currently is unavailable."

A particular public health concern surrounds cannabis effects on HIV/AIDS. Four studies among others may reduce related concern. Kaslow et al. (1989) demonstrated no evidence that cannabis accelerated immunodeficiency parameters in HIV-positive patients. Di Franco et al. (1996) ascertained no acceleration of HIV to full-blown AIDS in cannabis smokers. Whitfield, Bechtel and Starich (1997) observed no deleterious effects of cannabis usage in HIV/AIDS patients, even those with the lowest CD4 counts. Finally, Abrams et al. (2000) studied the effects of cannabis smoking on HIV positive patients on protease inhibitor drugs in a prospective randomized, partially blinded placebo-controlled trial. No adverse effects on CD4 counts were observed secondary to cannabis.

In our studies of four subjects (Table 4), Patient B had an elevated WBC count, probably attributable to the stress of phlebotomy, but without accompanying disorders of cell count differential. All patients had CD4 counts well within normal limits.

Review of Endocrine Function

Topical reviews of this topic are contained in two recent publications (Murphy 2001; Zimmer and Morgan 1997). As with other physiological systems, much data is based on animal studies, and early claims of deleterious effects on acute endocrine function are not necessarily supported by subsequent investigations or chronic use studies.

One long held claim is the production of gynecomastia in males associated with cannabis use. A case study or 3 cannabis smokers with this malady was reported by Harmon and Aliapoulios (1972). A more thorough investigation a few years later failed to show any differences in cannabis use in affected males between users and controls (Cates and Pope 1977).

Similarly, Kolodny et al. (1974) reported decreased testosterone levels in chronic marijuana smokers, while no differences in testosterone or luteinizing hormone (LH) levels were identified in a 3-week trial of smokers vs. non-smokers (Mendelson et al. 1978).

LH levels in menopausal women showed no significant changes after cannabis usage (Mendelson et al. 1985), but the next year, a similar group noted a 30% suppression of LH in women by smoking a single cannabis cigarette during the luteal phase (Mendelson et al. 1986).

Subsequently, a more in-depth study of both sexes was undertaken to assess multiple hormone effects comparing subjects with different levels of cannabis usage vs. controls (Block, Farinpour, and Schlechte 1991). No significant effects were noted on testosterone, LH, FSH, prolactin or cortisol in young women and men.

Jamaican chronic use studies were confined to examinations of thyroxine and steroid excretion with no significant findings observed due to cannabis use (Rubin and Comitas 1975).

In the 94-Day Cannabis Study, acute drops in testosterone and LH levels were noted after smoking a cannabis cigarette (Cohen 1976). Subsequent drops in testosterone levels were noted after the 5th week of daily usage. LH levels fell after the 4th week and FSH after the 8th week to unspecified degrees.

In Costa Rica, no differences were noted in male testosterone levels between abstainers and cannabis smokers stratified according to amount

of use (Carter 1980). Similarly, fertility was unimpaired, with both groups having identical numbers of progeny. The author stated (p. 172), "These findings cast serious doubt on cause-and-effect relationship between marihuana smoking and plasma testosterone level in long-term use."

Zimmer and Morgan (1997) summarized their observations by stating (p. 92), "There is no scientific evidence that marijuana delays adolescent sexual development, has a feminizing effect on males, or a masculinizing effect on females."

The latter statement would seem to be borne out by our findings. While one male subject had a minor degree of gynecomastia associated with obesity, none of the Patients A-D displayed any abnormal values in any endocrine measure (Table 5).

Patient A has two children, Patient B has three, and Patient D had one by choice.

Problems in the Compassionate IND Program

All four patients described varying degrees of logistical difficulties in obtaining their medicine. All have to travel or make special arrangements with their study physician, who is the arbiter of the potency of received material. All described incidents of inadequate supply or provision of inferior quality cannabis. All have had to supplement their supplies of cannabis from illegal black market sources at times.

All have experienced inconveniences or security concerns when traveling. One, Patient C, was arrested, detained, and had some of his medicine permanently confiscated without replacement.

Patients A-C decried the lack of an official identity card that might be readily recognized and accepted by law enforcement and security personnel. Rather, all used combinations of letters and other documents to convey their legal status to interested authorities, often to the accompaniment of much doubt and suspicion. All describe significant worry and anxiety about their medicine supplies, and whether official promises of continuation of the program will be honored.

A paramount issue affecting the Compassionate IND patients revolves around cannabis quality. It has been well established that recreational cannabis smokers prefer higher potency materials (Herning, Hooker, and Jones 1986; Chait and Burke 1994; Kelly et al. 1997). The same pertains for most clinical cannabis patients.

Chait and Pierri (1989) published a detailed analysis of NIDA marijuana cigarettes that is worthy of review in this context. NIDA mari-

juana is grown outside, one crop per biennium, harvested from a 5-acre facility at the University of Mississippi. Average yield of "manicured material" is 270 g per plant or 270 g per square foot (letter from NIDA, Steven Gust to Chris Conrad, August 18, 1999). Material is shipped to the Research Triangle Institute in North Carolina where it is chopped and rolled on modified tobacco cigarette machines, then stored partially dehydrated and frozen. Cigarettes average 800-900 g in weight. Material requires rehydration before usage, which the IND patients usually achieve by storage overnight in a refrigerated plastic bag with leaves of lettuce.

As of 1999 (letter, Steven Gust to EBR, June 7, 1999), NIDA had available cannabis cigarettes of 1.8%, 2.8%, 3.0%, and 3.4% THC, and bulk cannabis of up to 5% THC content. Other cannabinoid components were not quantitated. It was further stated that the strongest material was not provided to patients in their cigarette shipments because it was too sticky and would interfere with the rolling machine's functioning (Personal Communication to EBR, Steven Gust, December 1999).

Static burn rates of NIDA cannabis cigarettes were inversely related to potency (Chait and Pierri 1989), while the number of puffs that could be drawn from each cigarette averaged 8.8. While total particulate matter increased with potency, arguably less smoked material is necessary for medicinal effect. Of more concern, carbon monoxide levels were highest in the lower potency material; that is, CO was inversely proportional to THC content. Finally, test subjects in their study of NIDA cannabis reported (pp. 66-67), "that the marijuana is inferior in sensory qualities (taste, harshness) than the marijuana that they smoke outside the laboratory. Some have stated that it was the worst marijuana they had ever sampled, or that it tasted 'chemically treated.' "

All the study patients criticize the paper employed to roll the cannabis cigarettes as harsh, and tasting poorly. NIDA cannabis cigarettes resemble Pall Mall® brand tobacco cigarettes without the logo (Figure 3).

All study patients clean their cannabis and re-roll the material to varying degrees, although at least one former IND patient, now deceased, used the NIDA cigarettes unaltered.

NIDA cannabis is shipped to patients in labeled metal canisters containing 300 cigarettes (Figure 4), and material is frequently two or more years old upon receipt. Even under optimal storage conditions, a certain degree of oxidation of cannabinoids can be expected (Grotenhermen 2001). Most consumers prefer a supply of cured cannabis that is as fresh as possible.

FIGURE 3. NIDA Joints/Pall-Mall ®

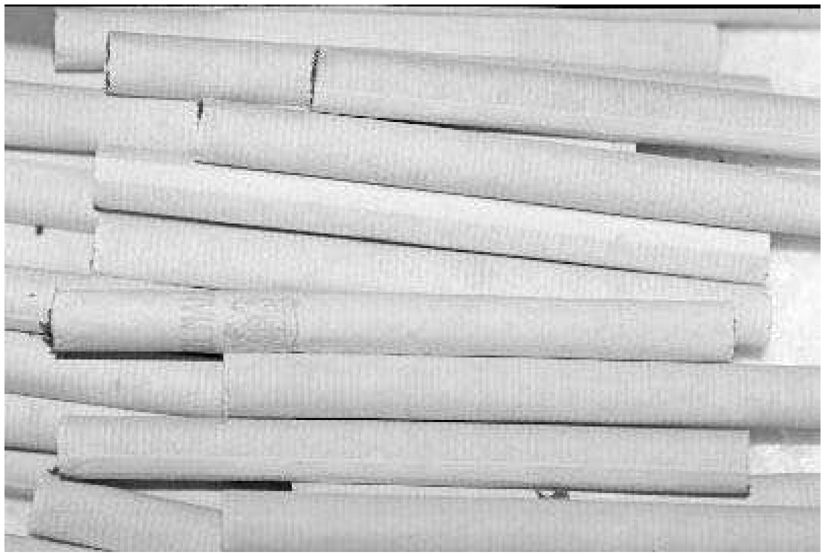
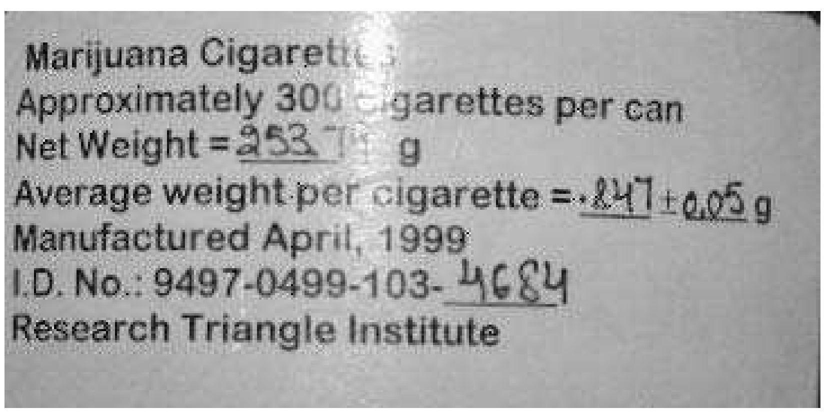


FIGURE 4. Steel Canister with Label



A close inspection of the contents of NIDA-supplied cannabis cigarettes reveals them to be a crude mixture of leaf with abundant stem and seed components (Figures 5-6). The odor is green and herbal in character. The resultant smoke is thick, acrid, and pervasive.

In contrast, a typical sinsemilla "bud" is seedless, covered with visi-

FIGURE 5. Loose NIDA Cannabis as Provided to Compassionate IND Patients

FIGURE 6. Close-Up of Debris from Three NIDA Cannabis Cigarettes

ble glandular trichomes (see journal cover), and emits a strong lemony or piney terpenoid scent. The smoke is also less disturbing from a sensory standpoint to most observers.

Whittle, Guy, and Robson (2001) describe in detail the markedly contrasting steps undertaken in a government approved clinical cannabis program in the United Kingdom. Their material is organically grown in soil with no chemical treatment under controlled indoor conditions. All male plants are eliminated, and only unfertilized female flowering tops are harvested for further processing. This material is assayed for cannabinoid and terpenoid content, with controlled ratios through genetic selection of seed strains before extraction. THC yields obtained are routinely 15-20% (Personal Communication, GW Pharmaceuticals, 2000).

Harm reduction techniques in relation to clinical cannabis consumption are well advanced (Russo 2001; Grotenhermen 2001a, 2001b). Particular attention is merited toward vaporization techniques that provide cannabinoid and terpenoid component administration to prospective clinical cannabis patients without pyrolysis (Gieringer 1996a; Gieringer 1996b; Gieringer 2001). Sublingual administration of cannabis extracts is another most promising technique of clinical cannabis administration (Whittle, Guy, and Robson 2001).

Three of the four study subjects have employed Marinol®, and found it inadequate or a poor substitute for cannabis in symptomatic relief of their clinical syndromes.

CONCLUSIONS AND RECOMMENDATIONS

1. Cannabis smoking, even of a crude, low-grade product, provides effective symptomatic relief of pain, muscle spasms, and intraocular pressure elevations in selected patients failing other modes of treatment.
2. These clinical cannabis patients are able to reduce or eliminate other prescription medicines and their accompanying side effects.
3. Clinical cannabis provides an improved quality of life in these patients.
4. The side effect profile of NIDA cannabis in chronic usage suggests some mild pulmonary risk.
5. No malignant deterioration has been observed.
6. No consistent or attributable neuropsychological or neurological deterioration has been observed.
7. No endocrine, hematological or immunological sequelae have been observed.

8. Improvements in a clinical cannabis program would include a ready and consistent supply of sterilized, potent, organically grown unfertilized female flowering top material, thoroughly cleaned of extraneous inert fibrous matter.
9. It is the authors' opinion that the Compassionate IND program should be reopened and extended to other patients in need of clinical cannabis.
10. Failing that, local, state and federal laws might be amended to provide regulated and monitored clinical cannabis to suitable candidates.

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Cannabinoids and Cystic Fibrosis: A Novel Approach to Etiology and Therapy

Ester Fride

ABSTRACT. Cannabis stimulates appetite and food intake. This property has been exploited to benefit AIDS and cancer patients suffering from wasting disease, by administering the whole plant or its major active ingredient Δ^9-tetrahydrocannabinol (THC).

Endogenous cannabinoids ("endocannabinoids") are found in maternal milk. We have recently shown that endocannabinoids are critical for milk ingestion and survival of newborns because blocking CB_1 receptors resulted in death from malnutrition.

Lack of appetite resulting in malnutrition is a contributing factor to mortality in many Cystic Fibrosis (CF) patients. It is proposed here for the first time, to administer THC to CF patients. It is hoped that the cannabinoid will alleviate malnutrition and thus help prevent wasting in CF patients.

Recent findings suggest that a lipid imbalance (high arachidonic acid/low DHA) is a primary factor in the etiology of CF and that defective CFTR (CF transmembrane conductor regulator) that characterizes the CF condition is responsible for the dysregulation. Endocannabinoids are all fatty acid derivatives. Therefore, it is further proposed here that the CFTR gene product also modulates endocannabinoid synthesis, through regulation of fatty acid biosynthesis. According to this hypothesis, CF patients display decreased levels of endocannabinoids and by elevating these levels, symptoms may improve. Indeed, a number of physiological mechanisms of cannabinoids and endocannabinoids coincide with the pathology of CF. Thus it is suggested that potential benefits from THC treatment, in addition to appetite stimulation, will include

Ester Fride, PhD, is Senior Lecturer at the Department of Behavioral Sciences and Head of the Laboratory of Behavioral Biology at the College of Judea and Samaria, Ariel, Israel 44837.

This paper is dedicated to Ies Fride (1952-2000) who fought to better the life of all CF patients

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antiemetic, bronchodilating, anti-inflammatory, anti-diarrheal and hypoalgesic effects.

KEYWORDS. Cannabis, cannabinoids, endocannabinoids, cystic fibrosis, appetite, wasting disease, fatty acids, medical marijuana

INTRODUCTION

Δ^9-tetrahydrocannabinol (THC) is the major psychotropic constituent of the cannabis (*Cannabis sativa*) plant. Since 1988, two specific receptors for Δ^9-THC have been discovered: CB_1, located in brain and other organs including lungs, blood vessels and spleen, and CB_2, located mainly in the periphery, notable the immune system (Ameri 1999). In 1992 the first endogenous ligand for the CB receptors was isolated from porcine brain and denoted "anandamide" (Devane et al. 1992). In 1995 and 2001, two additional major ligands were isolated from mammalian tissue, 2-arachidonylglycerol (2-AG) (Mechoulam et al. 1995) and "noladine" (Hanus et al. 2001). Collectively, the natural ligands of the CB receptors are called "endocannabinoids" and these three prototypes are derivatives of arachidonic acid (anandamide is an amide, 2-AG is an ester and noladine is an ether of arachidonic acid). Other ethanol amides of fatty acids with pharmacological activity, including docosatetraenyl ethanol amide and homo-g-linolenyl ethanol amide have been reported since the discovery of anandamide (Barg et al. 1993; Pertwee et al. 1994).

Appetite

Cannabis has been known for many years to enhance appetite and weight gain (Fride and Sanudo-Pena 2001; Fride and Mechoulam 2001). Anandamide has similar effects (Williams et al. 1998; 1999). Recent research in the medicinal aspects of marijuana has indicated that the plant may be used beneficially to combat wasting disease in AIDS and cancer patients (Mechoulam et al. 1998b). Indeed THC is used clinically for this purpose, particularly in AIDS patients (Beal et al. 1997).

We have reported previously that endocannabinoids are present in milk, with 2-arachidonylglycerol (2-AG) found in human milk in

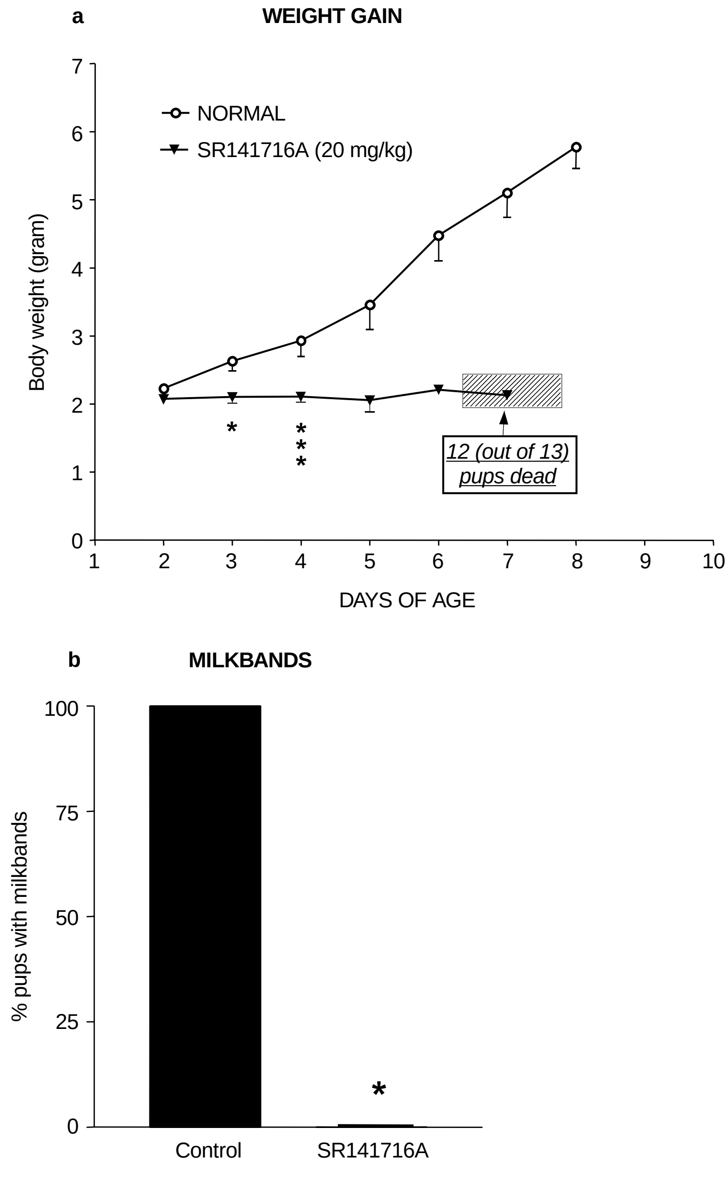
higher concentrations (8.7 ± 2.8 μg/g extracted lipids) than anandamide (0.0015 ± 0.003 μg/g) (Fride et al., 2001). We (Di Marzo et al. 1998) have also shown that 2-AG when administered orally, albeit in high doses, is active in the mouse 'tetrad,' a battery of tests that is used to assess central cannabimimetic activity (Martin et al. 1991; Fride and Mechoulam 1993). These findings suggest that 2-AG in maternal milk may reach, in part at least, the sucklings' central nervous system, thus possibly affecting appetite regulation, brain development and behavior.

Specific blockade of the cannabinoid (CB_1) receptor within the first 24 hr after birth completely abolishes the ability of newborn mice to ingest milk, as expressed in a complete failure to gain weight and an absence of "milkbands." (As the stomach area in mouse pups is transparent, due to lack of hair and the thinness of the skin, the amount of milk consumed can be observed as a "milk band.") Hence neonates exposed to a CB_1 receptor antagonist (SR141716A) did not survive the first week of life (Fride et al. 2001) (Figure 1).

This finding is compatible with the observation that the levels of the 2-AG in rodent pup brain, peak immediately after birth (Berrendero et al. 1999) and suggests a critical role for endocannnabinoids in milk intake and survival of newborns.

Cystic Fibrosis (CF) is the most prevalent lethal autosomal recessive disorder in the Caucasian population, affecting 1 in 2500 newborns (Collins 1992). A mutated form of the CFTR (CF transmembrane conductance regulator) gene is found CF patients (Zeitlin 2000). The disease is expressed as the formation of viscous secretions affecting several organs, mainly the lungs and the digestive system (Quinton 1999). Usually, a gradual decline in physiological functions is seen, eventually leading to death. Due to major strides over the years in palliative care, survival is expected to exceed 30 years (Resnikoff and Conrad 1998). Pulmonary dysfunction has long been considered the primary cause for morbidity and mortality in CF (Pilewski and Frizell 1999), with malnutrition appearing as a compounding detrimental factor (Borowitz 1996). More recently however, malnutrition is being recognized as playing a primary role in disease progression (Borowitz 1996; Schoni and Casaulta-Aebischer 2000) possibly even being responsible for lung pathology and infections (Yu et al., 2000). Thus in many CF patients, appetite reduction greatly accelerates the aggravation of the condition in its final stages (Anthony et al. 1999; Schoni and Casaulta-Aebischer 2000). Moreover, there is now evidence that im-

FIGURE 1. Effects on weight gain and milk ingestion of a single administration of SR141716A on the first day after birth. Mouse pup (Sabra, Harlan, Israel) littermates were injected sc within the first 24 hr after birth with SR141716A (20 mg/kg) or with vehicle (ethanol:emulphor:saline = 1:1:18) using 30G needles.



provement of the nutritional status *per se* may counteract the progression of lung disease (Shepherd et al. 1986; Dalzell et al. 1992).

Therefore, administration of cannabinoids may promote appetite, thus combating malnutrition and increasing chances for survival.

Side Effects of Cannabinoids During Development?

It is especially important to maintain growth in CF patients during the first years of life, because early malnutrition is associated with impaired cognitive development (Blecker et al., 2000). On the other hand, potential side effects of an appetite stimulant would be of particular concern at that stage. Interestingly, there is evidence from animal studies indicating that the developing organism does not display a central (psychotropic) response to THC administration (Fride and Mechoulam 1996), possibly because CB_1 receptors do not appear in high enough concentrations until adulthood (Rodriguez de Fonseca et al. 1993). Yet, Δ^8-THC (a stable metabolite of Δ^9-THC with similar activities) was a very effective antiemetic, while causing only minimal side effects in a clinical trial assessing the antiemetic effects of THC in children with hematological cancers (Abrahamov et al. 1995). These observations suggest that in the developing organism, while the psychotropic effects are not yet apparent, certain activities of cannabinoids are present including their antiemetic effects. In view of the critical role of endocannabinoids in feeding in the newborn (Fride et al. 2001), appetite enhancement is also likely to be present.

Fatty Acid Balance

A fatty acid imbalance is observed in CF patients, including elevated levels of arachidonic acid and reduced levels of docosahexanoic acid (DHA) (Gibson et al., 1986; Roulet et al., 1997), as well as in a knockout mouse model for CF (cftr$^{-/-}$ mice) (Freedman et al. 1999). The implications of this observation are far reaching. Heeckeren et al. (1997) have demonstrated that, in the absence of *a priori* lung disease, the lungs of cftr$^{-/-}$ mice displayed an excessive inflammatory response to *Pseudomonas aeruginosa*, resulting in increased pathology and mortality. Possibly, the increased levels of arachidonic acid are responsible for the excessive response (Freedman et al. 1999; Greener 2000). Furthermore, the low DHA levels have been shown to play a fundamental role in the pathogenesis in the organs affected by the CF disease: lungs, pan-

creas and ileum (Freedman et al. 1999). Thus, further decreasing DHA levels in cftr$^{-/-}$ mice worsened pathological manifestations, while elevating DHA levels by oral supplementation corrected the lipid imbalance and reversed the pathology of the affected organs. As a consequence it has been postulated that the mutated CFTR gene product is responsible for the lipid imbalance and the ensuing pathogenesis (Greener 2000).

Endocannabinoids and Cystic Fibrosis

Is it possible that the synthesis of endocannabinoids, being fatty acid derivatives, is also modulated by CFTR proteins? There are a number of striking parallels between the clinical manifestations of CF and the domains of cannabinoid and endocannabinoid influence, including lack of appetite, nausea, diarrhea, and lung disease. Low endocannabinoid levels could explain the appearance of these symptoms. However, even in the absence of a causative role, it is proposed here that by stimulating the cannabinoid system, some of the CF pathology symptoms may be alleviated. The potential for cannabinoids to enhance appetite, thereby possibly preventing malnutrition in CF has been described above. Below, a number of additional manifestations of CF and a possible therapeutic role for cannabinoids are described (Figure 2).

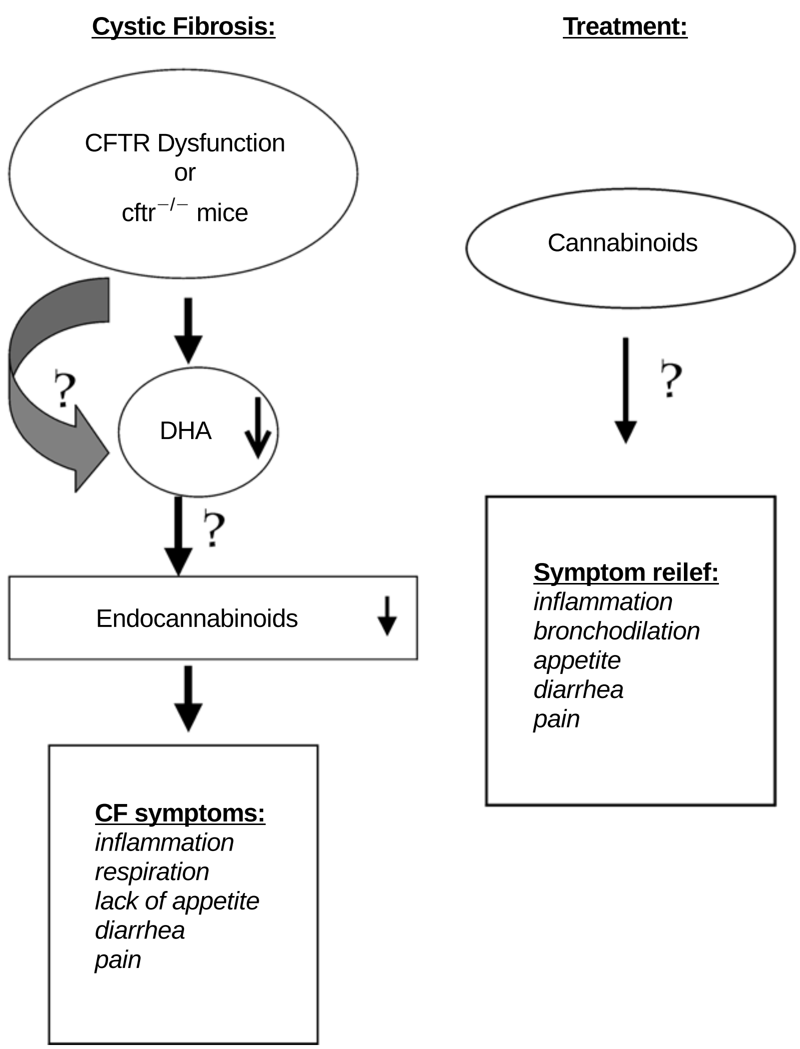
Antiemetic Effects

Vomiting induced by coughing (Blecker et al. 2000) often exacerbates the development of malnutrition in cystic fibrosis. Antiemetic benefits of THC have been demonstrated in its effective relief of chemotherapy-induced nausea and vomiting (Mechoulam et al., 1998b; Abrahamov et al. 1995). Therefore the antiemetic potential of cannabinoids would be expected to contribute to appetite enhancement induced by cannabinoids in CF patients.

Diarrhea

Diarrhea appears in CF as a result of inadequate digestion due to pancreatic insufficiency (Rolles 1998). Cannabinoids inhibit intestinal motility via local CB_1 (Colombo et al. 1998; Tyler et al. 2000) and/or via CB_2 (Fride 1995; Hanus et al. 1999) receptors. Therefore administration of cannabinoids to CF patients may counteract diarrhea and thereby help prevent loss of nutrients.

FIGURE 2. Hypothesis for pathogenesis and therapeutic approach to cystic fibrosis. Mutated CFTR gene products result in a lipid imbalance: high arachidonic acid/low docosahexanoic acid (DHA) and consequently in low endocannabinoid levels. Alternatively, the mutated CFTR results in low endocannabinoid levels in parallel to the lipid imbalance. The ensuing manifestations of CF are relieved by endocannabinoid treatment



Inflammation

Most destruction of lung tissue in CF is now thought to be secondary to a very aggressive neutrophilic inflammatory response (Konstan & Berger 1997; Wagener et al. 1997). This ultimately leads to respiratory failure. The antiinflammatory potential of cannabinoids is well documented (Klein et al. 2000; Straus 2001) and is thought to occur by interference with the arachidonic acid-eicosanoid synthetic pathways (McPartland 2001). We have demonstrated in a mouse model of arachidonic acid-induced ear inflammation that cannabinoids and endocannabinoids are effective antiinflammatory agents acting via CB receptors (Hanus et al. 1999; Fride et al. unpublished observations). Since cannabinoid receptors are present in lungs (Calignano et al. 2000), THC may be of additional benefit for CF patients, by reducing inflammatory processes in the lungs.

Lungs

It has been demonstrated recently that bronchodilating and cough-reducing activity of endocannabinoids in irritated lungs are mediated by local CB_1 receptors (Calignano et al. 2000). Therefore cannabinoids may also benefit CF patients by their bronchodilating and cough suppressing effects.

Pain

CF patients suffer pain from a variety of sources (Ravilly et al. 1996) including abdominal pain related to steatorrhea and malabsorption (Zeltzer et al. 1996), chest pain due to impacted sputum, pleuritic involvement with lung inflammation and infection, or chest wall pain associated with developing kyphoscoliosis and decreased chest wall mobility (Massie et al. 1998). Pain may also occur from gall bladder or kidney stones or from osteoporosis (Haworth et al. 1999; Lambert 2000; Ravilly et al. 1996). Cannabinoids are analgesics effective in a variety of conditions (Mechoulam et al. 1998b; Martin and Lichtman 1998), acting via cannabinoid receptors within as well as outside the brain and spinal cord and suppressing both acute and chronic pain (Pertwee 2001).

Route of Administration

Due to the severe lung pathology that develops in CF patients (Pilewski and Frizell 1999), cannabis smoking is contraindicated, de-

spite it being a preferred route in conditions such as multiple sclerosis (Iversen 2000; Mechoulam et al. 1998b). However, THC administered orally has been shown to effectively reduce vomiting and nausea in children undergoing chemotherapy for hematological cancers (Abrahamov et al. 1995). Additional routes are available and/or are being explored at this time (Gieringer 2001), which may be applicable to CF patients in the future. These include rectal suppositories (Mattes et al. 1994), transdermal patches (Gieringer 2001; Hu 2000) and smoke-free inhalation systems (Iversen 2000). The latter method may be of particular relevance when bronchodilating and local antiinflammatory effects in the lungs are primary therapeutic aims. Novel, effective vaporizers are currently under investigation.

CONCLUSIONS

In this paper a novel therapeutic target for cannabis is proposed, based on recent developments in research on cannabis on one hand, and on research on cystic fibrosis on the other. Recent findings suggest that the primary factors in the pathogenesis of CF includes fatty acid imbalance, possibly leading to such major manifestations of CF as chronic inflammation of the lungs and pancreatic disease (Greener 2000; Freedman et al. 1999). In the final stages of the disease malnutrition accompanied by a lack of appetite is frequently seen (Anthony et al. 1999; Schoni and Casaulta-Aebischer 2000). Additional symptoms of the disease may include pain due to a variety of sources (Ravilly et al. 1996), diarrhea (Rolles 1998) and nausea (Blecker et al. 2000).

Intriguingly, the therapeutic effects of cannabinoids include the potential to counteract each of these conditions. Thus appetite enhancement (Beal et al. 1997) and a critical role in food ingestion (Fride et al. 2001), analgesic, antiemetic, antiinflammatory, inhibition of intestinal motility and bronchodilating effects have been demonstrated (Calignano et al. 2001; Colombo et al. 1998; Fride 1995; Mechoulam et al. 1998b; Hanus et al. 1999; Tyler et al. 2000).

The major endocannnabinoids are structurally similar to arachidonic acid (Mechoulam et al. 1998a; Hanus et al. 2001) and dietary supplementation of essential fatty acids is associated with increased levels of endocannabinoids in piglets (Berger et al., 2001). Thus a more fundamental role of endocannabinoids in CF disease progression should be investigated. It has been proposed previously that a lipid imbalance

(high arachidonic acid/low DHA) is a major step in the pathogenesis of CF.

Therefore supplementing DHA in the diet should improve disease manifestations (Freedman et al. 1999; Greener 2000). However, dietary supplementation of DHA to improve the imbalance has proven difficult. Bioavailability is impeded by pancreatic insufficiency in CF patients and by adverse effects of additional fatty acids present in the formulation (Greener 2000).

It is proposed here, that CFTR not only regulates fatty acid balance but also endocannabinoid biosynthesis. Such mechanism predicts that low levels of endocannabioids in CF patients and in cftr$^{-/-}$ mice will be found, which could be responsible for many symptoms. It is hoped that affirmative data will eventually lead to the use of cannabinoids at more initial stages of cystic fibrosis (Figure 2).

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Cannabinoids and Cystic Fibrosis: A Novel Approach to Etiology and Therapy

Ester Fride

ABSTRACT. Cannabis stimulates appetite and food intake. This property has been exploited to benefit AIDS and cancer patients suffering from wasting disease, by administering the whole plant or its major active ingredient Δ^9-tetrahydrocannabinol (THC).

Endogenous cannabinoids ("endocannabinoids") are found in maternal milk. We have recently shown that endocannabinoids are critical for milk ingestion and survival of newborns because blocking CB_1 receptors resulted in death from malnutrition.

Lack of appetite resulting in malnutrition is a contributing factor to mortality in many Cystic Fibrosis (CF) patients. It is proposed here for the first time, to administer THC to CF patients. It is hoped that the cannabinoid will alleviate malnutrition and thus help prevent wasting in CF patients.

Recent findings suggest that a lipid imbalance (high arachidonic acid/low DHA) is a primary factor in the etiology of CF and that defective CFTR (CF transmembrane conductor regulator) that characterizes the CF condition is responsible for the dysregulation. Endocannabinoids are all fatty acid derivatives. Therefore, it is further proposed here that the CFTR gene product also modulates endocannabinoid synthesis, through regulation of fatty acid biosynthesis. According to this hypothesis, CF patients display decreased levels of endocannabinoids and by elevating these levels, symptoms may improve. Indeed, a number of physiological mechanisms of cannabinoids and endocannabinoids coincide with the pathology of CF. Thus it is suggested that potential benefits from THC treatment, in addition to appetite stimulation, will include

Ester Fride, PhD, is Senior Lecturer at the Department of Behavioral Sciences and Head of the Laboratory of Behavioral Biology at the College of Judea and Samaria, Ariel, Israel 44837.

This paper is dedicated to Ies Fride (1952-2000) who fought to better the life of all CF patients

antiemetic, bronchodilating, anti-inflammatory, anti-diarrheal and hypoalgesic effects.

KEYWORDS. Cannabis, cannabinoids, endocannabinoids, cystic fibrosis, appetite, wasting disease, fatty acids, medical marijuana

INTRODUCTION

Δ^9-tetrahydrocannabinol (THC) is the major psychotropic constituent of the cannabis (*Cannabis sativa*) plant. Since 1988, two specific receptors for Δ^9-THC have been discovered: CB_1, located in brain and other organs including lungs, blood vessels and spleen, and CB_2, located mainly in the periphery, notable the immune system (Ameri 1999). In 1992 the first endogenous ligand for the CB receptors was isolated from porcine brain and denoted "anandamide" (Devane et al. 1992). In 1995 and 2001, two additional major ligands were isolated from mammalian tissue, 2-arachidonylglycerol (2-AG) (Mechoulam et al. 1995) and "noladine" (Hanus et al. 2001). Collectively, the natural ligands of the CB receptors are called "endocannabinoids" and these three prototypes are derivatives of arachidonic acid (anandamide is an amide, 2-AG is an ester and noladine is an ether of arachidonic acid). Other ethanol amides of fatty acids with pharmacological activity, including docosatetraenyl ethanol amide and homo-g-linolenyl ethanol amide have been reported since the discovery of anandamide (Barg et al. 1993; Pertwee et al. 1994).

Appetite

Cannabis has been known for many years to enhance appetite and weight gain (Fride and Sanudo-Pena 2001; Fride and Mechoulam 2001). Anandamide has similar effects (Williams et al. 1998; 1999). Recent research in the medicinal aspects of marijuana has indicated that the plant may be used beneficially to combat wasting disease in AIDS and cancer patients (Mechoulam et al. 1998b). Indeed THC is used clinically for this purpose, particularly in AIDS patients (Beal et al. 1997).

We have reported previously that endocannabinoids are present in milk, with 2-arachidonylglycerol (2-AG) found in human milk in

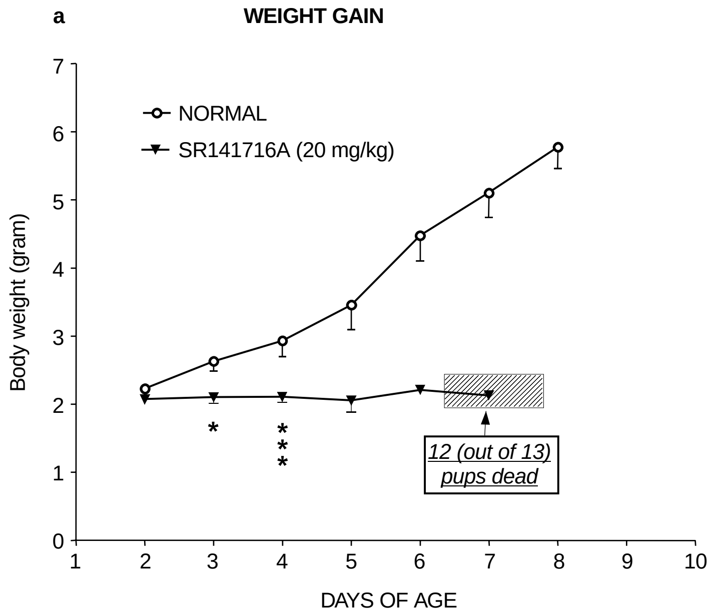
higher concentrations (8.7 ± 2.8 µg/g extracted lipids) than anandamide (0.0015 ± 0.003 µg/g) (Fride et al., 2001). We (Di Marzo et al. 1998) have also shown that 2-AG when administered orally, albeit in high doses, is active in the mouse 'tetrad,' a battery of tests that is used to assess central cannabimimetic activity (Martin et al. 1991; Fride and Mechoulam 1993). These findings suggest that 2-AG in maternal milk may reach, in part at least, the sucklings' central nervous system, thus possibly affecting appetite regulation, brain development and behavior.

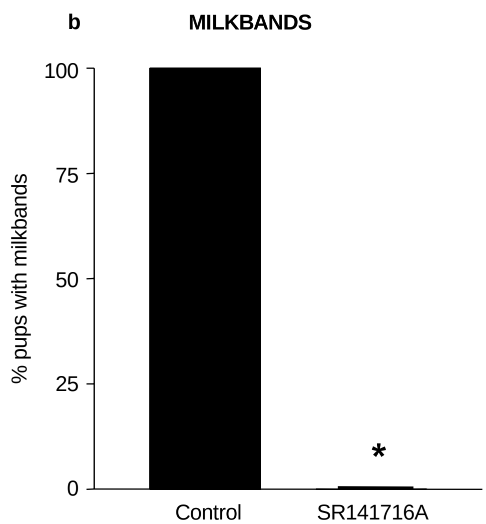
Specific blockade of the cannabinoid (CB_1) receptor within the first 24 hr after birth completely abolishes the ability of newborn mice to ingest milk, as expressed in a complete failure to gain weight and an absence of "milkbands." (As the stomach area in mouse pups is transparent, due to lack of hair and the thinness of the skin, the amount of milk consumed can be observed as a "milk band.") Hence neonates exposed to a CB_1 receptor antagonist (SR141716A) did not survive the first week of life (Fride et al. 2001) (Figure 1).

This finding is compatible with the observation that the levels of the 2-AG in rodent pup brain, peak immediately after birth (Berrendero et al. 1999) and suggests a critical role for endocannnabinoids in milk intake and survival of newborns.

Cystic Fibrosis (CF) is the most prevalent lethal autosomal recessive disorder in the Caucasian population, affecting 1 in 2500 newborns (Collins 1992). A mutated form of the CFTR (CF transmembrane conductance regulator) gene is found CF patients (Zeitlin 2000). The disease is expressed as the formation of viscous secretions affecting several organs, mainly the lungs and the digestive system (Quinton 1999). Usually, a gradual decline in physiological functions is seen, eventually leading to death. Due to major strides over the years in palliative care, survival is expected to exceed 30 years (Resnikoff and Conrad 1998). Pulmonary dysfunction has long been considered the primary cause for morbidity and mortality in CF (Pilewski and Frizell 1999), with malnutrition appearing as a compounding detrimental factor (Borowitz 1996). More recently however, malnutrition is being recognized as playing a primary role in disease progression (Borowitz 1996; Schoni and Casaulta-Aebischer 2000) possibly even being responsible for lung pathology and infections (Yu et al., 2000). Thus in many CF patients, appetite reduction greatly accelerates the aggravation of the condition in its final stages (Anthony et al. 1999; Schoni and Casaulta-Aebischer 2000). Moreover, there is now evidence that im-

FIGURE 1. Effects on weight gain and milk ingestion of a single administration of SR141716A on the first day after birth. Mouse pup (Sabra, Harlan, Israel) littermates were injected sc within the first 24 hr after birth with SR141716A (20 mg/kg) or with vehicle (ethanol:emulphor:saline = 1:1:18) using 30G needles.





provement of the nutritional status *per se* may counteract the progression of lung disease (Shepherd et al. 1986; Dalzell et al. 1992).

Therefore, administration of cannabinoids may promote appetite, thus combating malnutrition and increasing chances for survival.

Side Effects of Cannabinoids During Development?

It is especially important to maintain growth in CF patients during the first years of life, because early malnutrition is associated with impaired cognitive development (Blecker et al., 2000). On the other hand, potential side effects of an appetite stimulant would be of particular concern at that stage. Interestingly, there is evidence from animal studies indicating that the developing organism does not display a central (psychotropic) response to THC administration (Fride and Mechoulam 1996), possibly because CB_1 receptors do not appear in high enough concentrations until adulthood (Rodriguez de Fonseca et al. 1993). Yet, Δ^8-THC (a stable metabolite of Δ^9-THC with similar activities) was a very effective antiemetic, while causing only minimal side effects in a clinical trial assessing the antiemetic effects of THC in children with hematological cancers (Abrahamov et al. 1995). These observations suggest that in the developing organism, while the psychotropic effects are not yet apparent, certain activities of cannabinoids are present including their antiemetic effects. In view of the critical role of endocannabinoids in feeding in the newborn (Fride et al. 2001), appetite enhancement is also likely to be present.

Fatty Acid Balance

A fatty acid imbalance is observed in CF patients, including elevated levels of arachidonic acid and reduced levels of docosahexanoic acid (DHA) (Gibson et al., 1986; Roulet et al., 1997), as well as in a knockout mouse model for CF (cftr$^{-/-}$ mice) (Freedman et al. 1999). The implications of this observation are far reaching. Heeckeren et al. (1997) have demonstrated that, in the absence of *a priori* lung disease, the lungs of cftr$^{-/-}$ mice displayed an excessive inflammatory response to *Pseudomonas aeruginosa*, resulting in increased pathology and mortality. Possibly, the increased levels of arachidonic acid are responsible for the excessive response (Freedman et al. 1999; Greener 2000). Furthermore, the low DHA levels have been shown to play a fundamental role in the pathogenesis in the organs affected by the CF disease: lungs, pan-

creas and ileum (Freedman et al. 1999). Thus, further decreasing DHA levels in cftr$^{-/-}$ mice worsened pathological manifestations, while elevating DHA levels by oral supplementation corrected the lipid imbalance and reversed the pathology of the affected organs. As a consequence it has been postulated that the mutated CFTR gene product is responsible for the lipid imbalance and the ensuing pathogenesis (Greener 2000).

Endocannabinoids and Cystic Fibrosis

Is it possible that the synthesis of endocannabinoids, being fatty acid derivatives, is also modulated by CFTR proteins? There are a number of striking parallels between the clinical manifestations of CF and the domains of cannabinoid and endocannabinoid influence, including lack of appetite, nausea, diarrhea, and lung disease. Low endocannabinoid levels could explain the appearance of these symptoms. However, even in the absence of a causative role, it is proposed here that by stimulating the cannabinoid system, some of the CF pathology symptoms may be alleviated. The potential for cannabinoids to enhance appetite, thereby possibly preventing malnutrition in CF has been described above. Below, a number of additional manifestations of CF and a possible therapeutic role for cannabinoids are described (Figure 2).

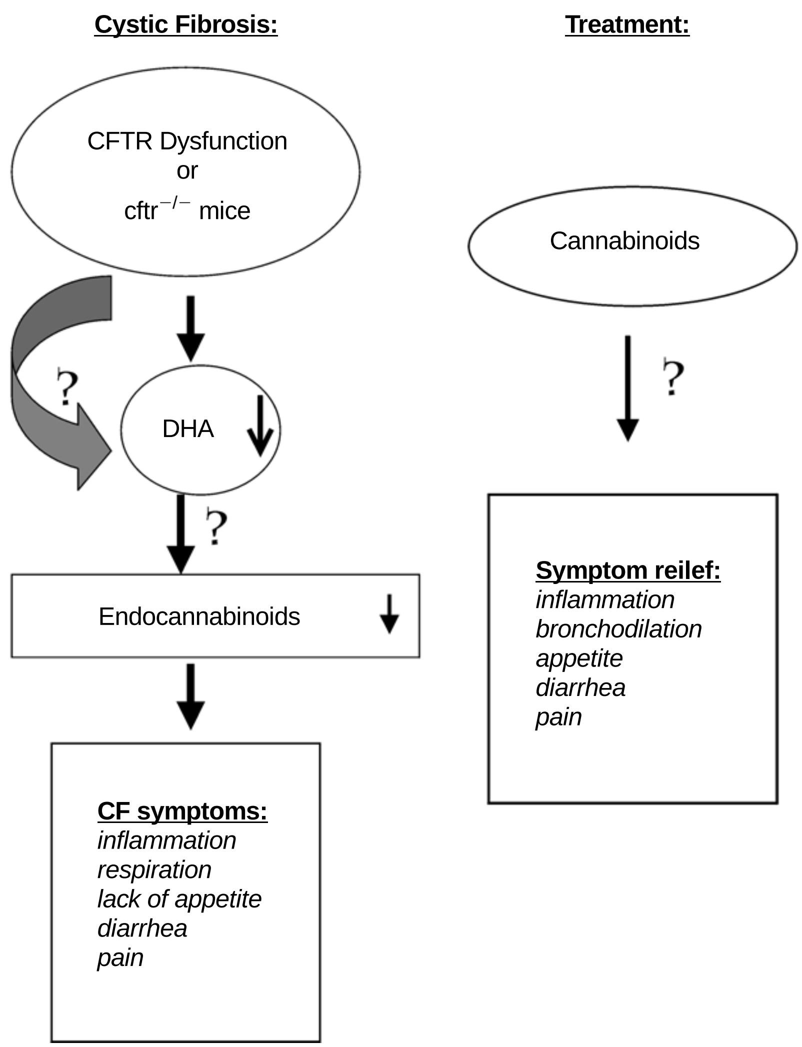
Antiemetic Effects

Vomiting induced by coughing (Blecker et al. 2000) often exacerbates the development of malnutrition in cystic fibrosis. Antiemetic benefits of THC have been demonstrated in its effective relief of chemotherapy-induced nausea and vomiting (Mechoulam et al., 1998b; Abrahamov et al. 1995). Therefore the antiemetic potential of cannabinoids would be expected to contribute to appetite enhancement induced by cannabinoids in CF patients.

Diarrhea

Diarrhea appears in CF as a result of inadequate digestion due to pancreatic insufficiency (Rolles 1998). Cannabinoids inhibit intestinal motility via local CB_1 (Colombo et al. 1998; Tyler et al. 2000) and/or via CB_2 (Fride 1995; Hanus et al. 1999) receptors. Therefore administration of cannabinoids to CF patients may counteract diarrhea and thereby help prevent loss of nutrients.

FIGURE 2. Hypothesis for pathogenesis and therapeutic approach to cystic fibrosis. Mutated CFTR gene products result in a lipid imbalance: high arachidonic acid/low docosahexanoic acid (DHA) and consequently in low endocannabinoid levels. Alternatively, the mutated CFTR results in low endocannabinoid levels in parallel to the lipid imbalance. The ensuing manifestations of CF are relieved by endocannabinoid treatment



Inflammation

Most destruction of lung tissue in CF is now thought to be secondary to a very aggressive neutrophilic inflammatory response (Konstan & Berger 1997; Wagener et al. 1997). This ultimately leads to respiratory failure. The antiinflammatory potential of cannabinoids is well documented (Klein et al. 2000; Straus 2001) and is thought to occur by interference with the arachidonic acid-eicosanoid synthetic pathways (McPartland 2001). We have demonstrated in a mouse model of arachidonic acid-induced ear inflammation that cannabinoids and endocannabinoids are effective antiinflammatory agents acting via CB receptors (Hanus et al. 1999; Fride et al. unpublished observations). Since cannabinoid receptors are present in lungs (Calignano et al. 2000), THC may be of additional benefit for CF patients, by reducing inflammatory processes in the lungs.

Lungs

It has been demonstrated recently that bronchodilating and cough-reducing activity of endocannabinoids in irritated lungs are mediated by local CB_1 receptors (Calignano et al. 2000). Therefore cannabinoids may also benefit CF patients by their bronchodilating and cough suppressing effects.

Pain

CF patients suffer pain from a variety of sources (Ravilly et al. 1996) including abdominal pain related to steatorrhea and malabsorption (Zeltzer et al. 1996), chest pain due to impacted sputum, pleuritic involvement with lung inflammation and infection, or chest wall pain associated with developing kyphoscoliosis and decreased chest wall mobility (Massie et al. 1998). Pain may also occur from gall bladder or kidney stones or from osteoporosis (Haworth et al. 1999; Lambert 2000; Ravilly et al. 1996). Cannabinoids are analgesics effective in a variety of conditions (Mechoulam et al. 1998b; Martin and Lichtman 1998), acting via cannabinoid receptors within as well as outside the brain and spinal cord and suppressing both acute and chronic pain (Pertwee 2001).

Route of Administration

Due to the severe lung pathology that develops in CF patients (Pilewski and Frizell 1999), cannabis smoking is contraindicated, de-

spite it being a preferred route in conditions such as multiple sclerosis (Iversen 2000; Mechoulam et al. 1998b). However, THC administered orally has been shown to effectively reduce vomiting and nausea in children undergoing chemotherapy for hematological cancers (Abrahamov et al. 1995). Additional routes are available and/or are being explored at this time (Gieringer 2001), which may be applicable to CF patients in the future. These include rectal suppositories (Mattes et al. 1994), transdermal patches (Gieringer 2001; Hu 2000) and smoke-free inhalation systems (Iversen 2000). The latter method may be of particular relevance when bronchodilating and local antiinflammatory effects in the lungs are primary therapeutic aims. Novel, effective vaporizers are currently under investigation.

CONCLUSIONS

In this paper a novel therapeutic target for cannabis is proposed, based on recent developments in research on cannabis on one hand, and on research on cystic fibrosis on the other. Recent findings suggest that the primary factors in the pathogenesis of CF includes fatty acid imbalance, possibly leading to such major manifestations of CF as chronic inflammation of the lungs and pancreatic disease (Greener 2000; Freedman et al. 1999). In the final stages of the disease malnutrition accompanied by a lack of appetite is frequently seen (Anthony et al. 1999; Schoni and Casaulta-Aebischer 2000). Additional symptoms of the disease may include pain due to a variety of sources (Ravilly et al. 1996), diarrhea (Rolles 1998) and nausea (Blecker et al. 2000).

Intriguingly, the therapeutic effects of cannabinoids include the potential to counteract each of these conditions. Thus appetite enhancement (Beal et al. 1997) and a critical role in food ingestion (Fride et al. 2001), analgesic, antiemetic, antiinflammatory, inhibition of intestinal motility and bronchodilating effects have been demonstrated (Calignano et al. 2001; Colombo et al. 1998; Fride 1995; Mechoulam et al. 1998b; Hanus et al. 1999; Tyler et al. 2000).

The major endocannnabinoids are structurally similar to arachidonic acid (Mechoulam et al. 1998a; Hanus et al. 2001) and dietary supplementation of essential fatty acids is associated with increased levels of endocannabinoids in piglets (Berger et al., 2001). Thus a more fundamental role of endocannabinoids in CF disease progression should be investigated. It has been proposed previously that a lipid imbalance

(high arachidonic acid/low DHA) is a major step in the pathogenesis of CF.

Therefore supplementing DHA in the diet should improve disease manifestations (Freedman et al. 1999; Greener 2000). However, dietary supplementation of DHA to improve the imbalance has proven difficult. Bioavailability is impeded by pancreatic insufficiency in CF patients and by adverse effects of additional fatty acids present in the formulation (Greener 2000).

It is proposed here, that CFTR not only regulates fatty acid balance but also endocannabinoid biosynthesis. Such mechanism predicts that low levels of endocannabioids in CF patients and in cftr$^{-/-}$ mice will be found, which could be responsible for many symptoms. It is hoped that affirmative data will eventually lead to the use of cannabinoids at more initial stages of cystic fibrosis (Figure 2).

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Sourcing the Code: Searching for the Evolutionary Origins of Cannabinoid Receptors, Vanilloid Receptors, and Anandamide

John M. McPartland
Patty Pruitt

ABSTRACT. Two cannabinoid (CB) receptors are known in humans, CB_1 and CB_2. They are phylogenetically ancient. Studies suggest CB receptors occur in mammals, birds, amphibians, fish, sea urchins, mollusks, leeches, and *Hydra vulgaris*. The CB receptor genes from some of these animals have been cloned and sequenced. These sequences were used to construct a phylogenetic tree of CB genes. The gene tree is rooted in an ancestral CB gene that predates the divergence of vertebrates and invertebrates. Thus the primordial CB receptor evolved at least 600 million years ago, a date broadly consistent with the Cambrian explosion. Since then, one clade of invertebrates, the Ecdysozoa, has secondarily lost the genes coding CB receptors. There is no evidence that animals obtained CB genes from other organisms via horizontal gene transfer. We hypothesize that the primordial CB receptor diverged from a related G-protein coupled receptor, and it linked with a pre-existing ligand, anandamide. Anandamide serves as a ligand for CB receptors as well as vanilloid (VR) receptors. VR receptors regulate the sensation of pain, and may also modulate mood and memory. Our phylogenetic analysis suggests that VR receptors evolved before CB receptors, so anandamide first served as a VR ligand. We speculate that CB receptors, lacking se-

John M. McPartland, GW Pharmaceuticals, Ltd., Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, United Kingdom.

Patty Pruitt, Faculty of Health & Environmental Science, UNITEC, Private Bag 92025, Auckland, New Zealand.

Address correspondence to: Patty Pruitt at the above address (E-mail: jmcpartland@unitec.ac.nz).

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lective constraints, subsequently acquired a mutation that coupled them with 2-AG. A better understanding of CB and VR receptors man enable us to combine their beneficial effects. Dual-signaling ligands such as anandamide have excellent therapeutic potential as analgesics, vasodilators, and anti-cancer agents.

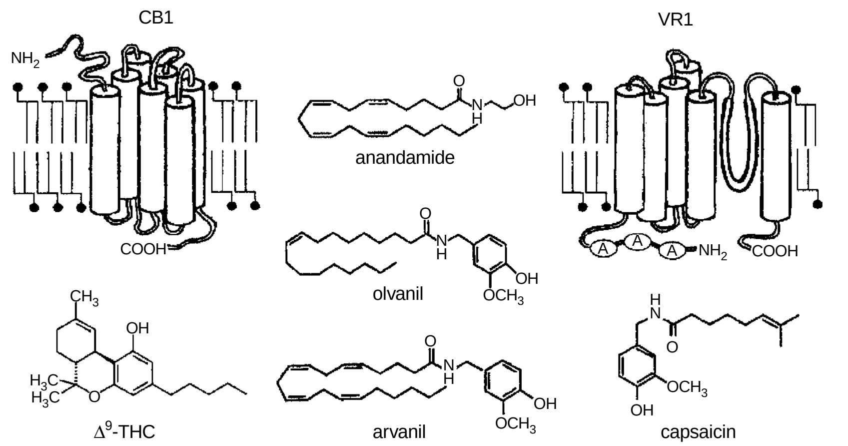
KEYWORDS. Cannabis, cannabinoids, vanilloids, G-protein coupled receptors, anandamide, horizontal gene transfer

INTRODUCTION

Cannabis and Cannabinoid Receptors

The capacity of cannabis to alter human consciousness was discovered at least 12,000 years ago (Abel 1980). More recently, Gaoni and Mechoulam (1964) isolated Δ^9-tetrahydrocannabinol (Δ^9-THC) as the primary psychoactive ingredient in cannabis. Because Δ^9-THC is highly lipophilic, it can act as a solvent on cell membranes. Researchers initially thought it simply "sloshed" neurons in a very nonspecific manner, like alcohol. Following the discovery of opioid receptors, however, Devane et al. (1988) demonstrated that cannabinoids bind to a selective, high-affinity membrane receptor. The cannabinoid receptor (now termed CB_1) was cloned, and its DNA sequence uncoded (Matsuda et al. 1990). The human gene encoding CB_1, *CNR1,* is a nucleotide sequence 1755 base pairs (bp) in length, and translates into a protein consisting of 472 amino acids (reviewed by Felder and Glass 1998). The chain of amino acids winds into a series of seven transmembrane domains (α-helices), connected by alternating intra- and extracellular loops, terminating with an extracellular amino group and an intracellular carboxyl group (Figure 1). This serpentine topology is characteristic of all G-protein-coupled receptors (GPCRs), such as the receptors for endothelial sphingolipids (EDG-1), melanocortin, adenosine, some glutamate receptors, acetylcholine (muscarinic, but not nicotinic receptors), serotonin (all 5-HT classes except 5-HT_3), epinephrine (alpha- and beta-adrenergic receptors), $GABA_B$, dopamine, opioids, ACTH, CCK, VIP, FSH, LH, TSH, parathyroid hormone, calcitonin, glucagon, oxytocin, vasopressin, angiotensin II, and substance P.

FIGURE 1. Schematic illustrations of CB1 and VR1 receptors, with examples of endogenous and exogenous ligands.



A second CB receptor, termed CB_2, was discovered by Munro, Thomas, and Abu-Shaar (1993). The CB_2 gene, *CNR2,* codes for a nucleotide sequence 1776 bp in length, and translates into a protein consisting of 360 amino acids. When the sequences of *CNR1* and *CNR2* are aligned for comparison, Munro, Thomas, and Abu-Shaar (1993) reported that they are identical at only 44% of their translated amino acid residues.

CB Receptor Phylogenetics

Evidence suggests that CB receptors are phylogenetically ancient, because homologs of human CB receptors are found in many other animals. A homolog is defined in biological systematics as a similar structure, behavior, or other trait shared by different species. Homologous traits permit us to make inferences about a series of events that happened in the past, known as evolution, which cannot be directly observed. The concept of "homologous series" was described by Vavilov (1922). It was Vavilov's elucidation of homologous series that led to his breakthroughs in *Cannabis* plant taxonomy (Vavilov 1926).

In the field of phylogenetics, homologs are divided into two groups: *Orthologs* are homologous genes found in different organisms, derived by descent from a common ancestor. *Paralogs* are homologous genes found in a given organism, derived by a gene duplication event. Murphy

et al. (2001) cloned and sequenced *CNR1* orthologs from 62 species of placental mammals, sampled across all extant orders within that clade. *CNR1* orthologs have been cloned and sequenced from earlier vertebrates, including the zebra finch, *Taeniopygia guttata* (Soderstrom and Johnson 2000), the newt salamander, *Taricha granulosa* (Soderstrom et al. 2000), and the puffer fish, *Fugu rubripes* (Yamaguchi, Macrae, and Brenner 1996). The puffer fish expressed a pair of paralogs, *F* CB_1*A* and *F* CB_1*B*. CB_2 genes, which are paralogs of CB_1 genes, have not been well-studied in other animals. *CNR2* orthologs have been cloned from rodents (*Rattus norvegicus, Mus musculus*), but are absent in puffer fish (Yamaguchi, Macrae, and Brenner 1996).

Invertebrates may also express CB receptors; Stefano, Salzet, and Salzet (1997) cloned and sequenced a CB_1 gene fragment from the leech, *Hirudo medicinalis.* Unfortunately this has been the only attempt to clone a CB gene from an invertebrate. Other invertebrates display evidence of CB receptors, although the evidence is based on non-molecular methods, such as radioligand binding studies. This data set comprises the sea urchins *Strongylocentrotus purpuratus* and *Paracentrotus lividus,* the leech *Theromyzon tessulatum,* the mollusk *Mytilus edulis,* and even the most primitive animal with a nerve network, the cnidarian *Hydra vulgaris* (review by Salzet et al. 2000).

Conversely, other invertebrates *lack* CB receptors, as evidenced by genome studies and radioligand binding studies. McPartland, Glass, and Mercer (2000) screened the entire genome of the fruit fly *Drosophila melanogaster,* which had been recently sequenced (Rubin et al. 2000), and found no genes with sequences resembling those of *CNR1* and *CNR2.* Several low-identity sequences were located, but they exhibited crippling amino acid substitutions at critical residues known to confer CB receptor specificity. For example, in transmembrane helix 3 (Figure 2), CB_1 binding depends on a lysine residue at position 3.28 (Song and Bonner 1996) and a valine at 3.32 (Song et al. 1999); CB_2 receptors uniquely have key binding residues at methionine 3.34 (Chin et al. 1999), serine 3.31 and threonine 3.35 (Tao et al. 1999). The *D. melanogaster* sequences with closest identity to *CNR1* and *CNR2* had substitutions at all these positions.

Similarly, McPartland (2001) screened the entire genome of the nematode worm *Caenorhabditis elegans* and encountered similar crippling substitutions (Figure 2). These studies suggest the genes for CB receptors have been lost in *D. melanogaster* and *C. elegans,* or they mutated into unrecognizable psuedogenes. These negative results have been confirmed by radioligand binding studies of the insects *Apis mellifera*

FIGURE 2. Alignment of sequences in CB receptor transmembrane helix 3, from amino acid residues 3.23 to 3.52.

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	222222233333333334444444444555
	345678901234567890123456789012
HUMAN CB1	NVFLFKLGGVTASFTASVGSLFLTAIDRYI
RHESUS CB1	NVFLFKLGGVTASFTASVGSLFLTAIDRYI
RAT CB1	NVFLFKLGGVTASFTASVGSLFLTAIDRYI
MOUSE CB1	NVFLFKLGGVTASFTASVGSLFLTAIDRYI
FINCH CB1	NVFLFKLGGVTASFTASVGSLFLTAIDRYI
NEWT CB1	NVFLFKLGGVTASFTASVGSLFLTAIDRYI
FISH CB1A	NVFLFKLGGVTASFTASVGSLFLTAIDRYI
FISH CB1B	SIFLFKLAGVTASFTASVGSLFLTAIDRYV
LEECH CB1	NVFLFKLGGVTASHYASVGSIVLTAIDRYL
Drosophila CG9753	HACLFTVSLLVVLFTISIFCLVAVSVDRYW
C. elegans C02H7.2	IRNIVMIFFYDLFWYTGVVQLGLMAGNRFV
HUMAN CB2	AVFLLKIGSVIMTFTASVGSLLLTAIDRYL

The human CB1 sequence in this region is identical to the CB1 orthologs cloned from monkey, rat, mouse, finch, newt, and fish CB1A. Fish CB1B contains four substitutions, and leech CB1 contains five substitutions; substitutions are printed in reverse (white on black). *Drosophila* (fruit fly) and *C. elegans* (nematode worm) sequences determined by BLAST as most identical to CB1 (McPartland et al. 2000c, 2001) are rife with substitutions. The human CB2 sequence contains eight substitutions in this region. Amino acid residues known to confer CB1 receptor specificity, such as the lysine at 3.28 and valine at 3.32, are in long boxes. CB2-specific serine (3.31), methionine (3.34), and threonine (3.35), are in short boxes.

(McPartland, Mercer, and Glass 2000), *D. melanogaster* (McPartland, Glass, and Mercer 2000), *Gerris marginatus*, *Spodoptera frugiperda*, and *Zophobas atratus* (McPartland et al. 2001). The apparent lack of an endocannabinoid system in insects opens many experimental possibilities. To better understand the role of CB receptors in health and disease, perhaps insects can serve as experimental animals akin to knockout mice (Di Marzo et al. 2000).

Sourcing CB Receptors from Horizontal Gene Transfer

The discovery of CB receptors led to an enigmatic question: why do animals have receptors for a cannabis compound? Pirozynski (1988) suggested that these kinds of "puzzling phenomena" could be caused by horizontal gene transfer (HGT). HGT is the nonsexual transmission of DNA between genomes of unrelated, reproductively isolated organisms (Rosewich and Kistler 2000). Scientists steeped in Darwinian theory tend to dismiss the significance of HGT, perhaps because of its

Lamarckian attributes, i.e., the acquisition of inheritable traits from the environment (in this case, from other organisms in the environment). Nevertheless, the sequencing of over 20 prokaryote genomes since 1995 has revealed the importance of HGT in the Archaea (e.g., *Methanococcus jannaschii*, *Archaeoglobus fulgidus*), and the Bacteria (e.g., *Haemophilus influenzae*, *Escherichia coli*, *Xylella fastidiosa*). Over 200 human genes may have been obtained from bacteria via HGT (International Human Genome Sequencing Consortium 2001), although this estimate is controversial (Saltzbeg et al. 2001).

McEno et al. (1991) proposed that humans acquired CB genes via HGT, from *Cannabis sativa;* McEno conjectured that Δ^9-THC originally served as a ligand for CB receptors in the plant. HGT between distantly-related eukaryotes can be vectored by parasites capable of bridging both hosts. For example, the bacterium *Agrobacterium tumefaciens* is a potential vector, thanks to its extrachromosomal "Ti" plasmids, which are flawless gene conveyors. *A. tumefaciens* normally acts as a plant pathogen and it readily infects *Cannabis* spp. (McPartland, Clarke, and Watson 2000), but the pathogen also infects humans (Hulse, Johnson, and Ferrieri 1993). *A. tumefaciens* is capable of vectoring DNA into mammalian nuclei (Ziemienowicz et al. 1999), but the reverse also occurs. An ortholog of a human gene has been found in the bacterium (Whitehouse et al. 1998).

Fungi are potential HGT vectors; over a dozen fungal pathogens are known to infect both *Cannabis* spp. and humans (McPartland and Pruitt 1997). HGT among fungi may be quite common, and cases have been confirmed under experimental conditions (Rosewich and Kistler 2000). Incidences of HGT have been described between fungi and plants (e.g., the gene encoding taxol production, Stroble et al. 1996), and between fungi and animals (e.g., 6-hydroxynicotine oxidase, Schenk and Decker 1999).

Endogenous Cannabinoid Ligands

The HGT hypothesis lost some of its cachet when Devane et al. (1992) discovered an endogenous cannabinoid ligand that was produced in brain tissue, which they named anandamide (Figure 1). Since then, two other endogenous cannabinoid ligands have been found, *sn*-2 arachidonylglycerol (2-AG) (Mechoulam et al. 1995) and *sn*-2 arachidonylglyceryl ether (2-AGE) (Hanus et al. 2001). These compounds are called "endocannabinoids" (DiMarzo and Fontana 1995), to differenti-

ate them from exogenous, plant-derived "phytocannabinoids" (Pate 1999). Endocannabinoids display a profile of biological activities similar to that of Δ^9-THC, such as activation of CB receptors, inhibition of adenylate cyclase and calcium channels, hypothermia, analgesia, hypomobility, and catalepsy (Felder and Glass 1998). Endocannabinoids can explain why we have receptors that are sensitive to cannabis compounds; the plant ligands are simple mimics of our own, endogenous ligands.

The HGT hypothesis continues to have adherents. Ephick (1998) hypothesized a HGT mechanism to explain the existence of a CB gene in the leech. HGT may be implied by "puzzling phenomena" seen in other plants (other than *Cannabis* spp.). Soderstrom et al. (1998) discovered primitive plants (green algae) produce compounds that can bind to CB receptors. Tomato, soybean, and barley lipoxygenase enzymes can metabolize anandamide, a function that mammalian lipoxygenases cannot perform (van Zadelhoff, Veldink, and Vliegenhart 1998). Pine trees produce an analog of 2-AG, and the compound exhibits cannabimimetic activity (Nakane et al. 2000). These studies suggest many plants, presumably including *Cannabis* spp., can metabolize materials that have affinity for CB receptors. No one has looked to see if plants have the receptors.

Parallels Between Cannabis spp. and Capsicum spp.

The genus *Cannabis* evolved in central Asia. Presently the genus includes *C. sativa* L., *C. indica* Lamark, *C. ruderalis* Janischewsky, and *C. afghanica* Vavilov. About the same time that prehistoric humans discovered *Cannabis* spp., early Native Americans migrated across the Bering Strait land bridge, and moved into central America. There they encountered chili peppers, *Capsicum* spp., whose physiological effects were so desirable and habituating that chili pepper use permeated Mesoamerican culture for thousands of years. A physician to the fleet of Columbus brought chili peppers to Europe, and thereafter chili peppers spread worldwide. *Capsicum* spp. are now consumed daily by an estimated 25% of the world's population (Szallasi and Blumberg 1999).

The pungent, burning sensation is caused by capsaicin, a vanilloid compound (Figure 1). Capsaicin-sensitive nerves are a subset of sensory neurons, nociceptors that give rise to small diameter, unmyelinated C fibers (rarely, A δ fibers). Because capsaicin is highly lipophilic, researchers initially believed capsaicin worked in a nonspecific manner,

by perturbing neural membrane lipids. But once again, radioligand studies demonstrated that capsaicin binds to a selective membrane receptor, and the receptor was subsequently cloned (Caterina et al. 1997). Caterina and colleagues called it the vanilloid receptor, VR1. The topology of VR1 differs significantly from that of CB receptors; VR1 is a cation channel (Figure 1). The chain of amino acids in VR receptors is longer (consisting of 839 residues), and winds into a series of six transmembrane domains (β-sheets). The loop between transmembrane regions 5 and 6 forms a membrane pore, and the amino terminal contains three ankyrin domains. Both terminals are Intracellular.

VR1 conveys information about a variety of noxious stimuli. It is activated by capsaicin and other compounds, by moderate heat (> 43°C), and perhaps by protons (tissue acidosis). VR1 activation triggers Ca^{2+} influx, causing a cascade of local inflammatory and vasodilatory reactions. Ca^{2+} influx also causes membrane depolarization, potentially generating an action potential. The signal propagates to dorsal horn ganglia, evoking the release of somatostatin, substance P, and calcitonin gene related peptide (CGRP) within the dorsal horn (Szallasi and Blumberg 1999).

With repeated exposure to these stimuli, VR1 receptors become desensitized. This phenomenon partially underlies the seemingly paradoxical use of capsaicin as an analgesic. The daily oral consumption of chili peppers by indigenous people may provide symptomatic relief for chronic caries and poor dentition. Synthetic capsaicin has been used to treat post-herpetic neuralgia (shingles), osteo- and rheumatoid arthritis, diabetic neuropathy, post-surgical pain, interstitial cystitis, vasomotor rhinitis, cluster headaches, many other forms of hyperalgesia and allodynia (Szallasi and Blumberg 1999).

The Cannabinoid and Vanilloid Connection

There is evidence of cross-talk between CB receptors and VR receptors. The recent discovery of VR1 receptors in many brain regions (e.g., preoptic area, locus ceruleus, medial hypothalamus, striatum) suggests that VR1 receptors may modulate emotions and memory (Szallasi and DiMarzo 2000). Indeed, VR1 and CB_1 receptors may co-localize in the same neurons.

Significantly, anandamide acts as an agonist at VR1. No other endogenous ligands of VR1 have been discovered. Zygmunt et al. (1999) described anandamide as a partial VR1 agonist, whose affinity for VR1

nearly equals its affinity for CB_1. Smart et al. (2000) described anandamide as a full agonist at VR1, but reported its binding affinity was 20 times less potent at VR1 than at CB_1.

On the other side of the coin, olvanil, a synthetic ligand of VR1 (Figure 1), also serves as a CB_1 ligand (Di Marzo et al. 1998). Olvanil binds tighter to CB_1 (Ki = 1.6 µM) than does anandamide to CB_1 (Ki = 1.9 µM). Di Marzo et al. (2001) subsequently synthesized arvanil, a "hybrid" molecule that grafted the vanillyl ring of capsaicin onto the C20:4 omega 6 fatty acid moiety of anandamide (Figure 1). Arvanil has four times more affinity than anandamide at CB_1 (Ki = 0.25-0.52 and 1.9 µM, respectively), and three times more affinity than capsaicin at VR1 (Ki = 0.3 and 1.3 µM, respectively). This convolution of receptors and ligands of CB and VR has led to the suggestion that they might require unification under IUPHAR nomenclature (Szolcsányi 2000). Similar situations have arisen with glutamate, acetylcholine, GABA, and 5-HT receptors, all of which encompass metabotropic GCRPs as well as ionotropic channel receptors.

After Caterina et al. (1997) cloned and decoded VR1, they discovered a VR paralog (Caterina et al. 1999), the VR-like protein 1 (VRL-1). This receptor is not activated by vanilloid ligands or moderate heat; it responds to high temperatures (−52°C). Suzuki et al. (1999) subsequently cloned a VR paralog sensitive not to ligands or heat, but to mechanical pressure. They designated it the Stretch-Inhibitable Cation (SIC) channel. This gating mechanism is shared by the VR-related Osmotically Activated Channel (VR-OAC) (Liedtke et al. 2000). A flurry of VR-related receptors have been recently described, in some cases simultaneously by different labs, such as Liedtke et al. (2000) and Strotmann et al. (2000). Some VR receptors were described before their identity was recognized. The VRL-1 ortholog in the mouse was initially labeled a growth-factor-related channel (Kanzaki et al. 1999). A clade of VR-related receptors has been named Epithelial Ca^{2+} Channels (ECaC) (Hoenderop et al. 1999) and Ca^{2+} Transport channels (CaT1 and CaT2) (Peng et al. 1999). Most recently, Delany et al. (2001) identified VRL-2.

The functional coupling of CB and VR receptors is complex. Activation of CB_1 by anandamide is antinociceptive; it reduces capsaicin-evoked release of CGRP from the dorsal horn. Activation of VR1 by anandamide does just the opposite, in the same neurons (reviewed by Szolcsányl 2000). The fact that anandamide serves as a ligand for CB and VR receptors presents an evolutionary riddle: which receptor was the ligand's original target? Which was the inaugural receptor?

Purpose of This Study

The present study has three aims. First, it will examine the similarity between human CB genes and their homologs in other animals. CB gene sequences vary from species to species, due to accumulated mutations. For example, the CB_1 gene from the rhesus monkey (*Macaca mulatta*) is 100% identical to the human *CNR1* sequence, whereas the partial CB_1 gene cloned from the leech (*H. medicinalis*) shares only 58% identity with *CNR1*. Their percent identity is proportional to the evolutionary distances between them. The primordial ancestors of humans and leeches diverged at least 600 million years ago (Lee 1999), so CB genes in the two species had over half a billion years to accumulate differences. In contrast, the CB genes in humans and monkeys had only 10 million years to accumulate differences. These differences will be used to construct a gene tree of *CNR1*, *CNR2*, and their related paralogs and orthologs.

Second, the present study will search for evidence of HGT-mediated CB gene migration. We can test this hypothesis by conducting radioligand studies on plants, such as *C. sativa*, to see if plant tissues have specific binding sites for tritiated cannabinoids. Better yet, we can search for plant genes that resemble *CNR1* or *CNR2*; and the first plant to have its entire genome sequenced, *Arabidopsis thaliana*, has recently become available (Arabidopsis Genome Initiative 2000). The entire genomes of over 20 species of Bacteria and Archaea will also be scanned, in a search for potential HGT vectors.

Third, the CB versus VR question will be addressed. A VR gene tree will be constructed, and then compared to the CB gene tree, by quantifying their respective sequence divergences. Since the degree of sequence divergence is correlated with evolutionary time, this analysis should estimate the relative ages of CB genes and VR genes. It is assumed that anandamide originally evolved as the ligand of the older receptor.

MATERIALS AND METHODS

Construction of the CB Receptor Tree

The deduced amino acid sequences of curated *CNR1* and *CNR2* were obtained from GenBank™ (National Center for Biotechnology Information, www.ncbi.nlm.nih.gov), accession numbers g.i. 4502927 and

g.i. 4502929, respectively. They were compared to the deduced amino acid sequences of selected whole clones of CB gene homologs deposited in GenBank™, with the following accession (g.i.) numbers: rhesus monkey CB_1, 9664881; rat CB_1, 111475; mouse CB_1, 733425, finch CB_1, 8575561; newt CB_1, 8575561; puffer fish CB_1A, 2494952; puffer fish CB_1B, 2494952; rat CB_2, 10719923; and mouse CB_2, 7447152. The leech sequence was obtained from Stefano, Salzet, and Salzet (1997). Sequences were aligned using gapped BLAST (Basic Local Alignment Search Tool) version 2.0 (Altschul et al. 1997), also available on the Internet (www.ncbi.nlm.nih.gov/blast/).

Homologies were calculated as percent identity (identical amino acid residues), aligned over a designated length of amino acid residues. Protein homology is considered significant in the presence of at least 30% identity, aligned over a stretch of at least 80% of the sequence length (Rubin et al. 2000). Significant sequences identified by BLAST were considered orthologs if they had greater sequence identity to human CB genes than to any other sequences in that given organisms (Tatusov et al. 2000). BLAST 2.0 uses a “SEG program” as a default filter to eliminate low-complexity regions within sequences (i.e., amino acid repeats). This can confound BLAST searches with sequences that have low-complexity regions, such as the βχχβ repeat in CB_1 (Reggio et al. 2000). Thus, BLAST searches were run with the SEG filter off.

A gene tree of 12 CB gene homologs was assembled, its branching pattern based on the percentage sequence identity measured between *CNR1* and its paralogs and orthologs (Feng and Doolittle 1996). The CB gene tree contained little data concerning invertebrates, however, so the tree was supported with supplemental data obtained from whole-genome studies and non-molecular data. This data strongly implies the presence or absence of CB receptors in other organisms. The following non-vertebrates and their non-molecular data were compiled in the supplemental data: *H. vulgaris* specifically binds the selective CB_1 antagonist $[^3H]$SR141716A, produces anandamide, and exhibits FAAH activity (De Petrocellis et al. 1999). FAAH (fatty acid amide hydrolase) is the enzyme that degrades anandamide (Duetsch and Chin 1993). *S. purpuratus* binds the synthetic CB ligand $[^3H]$CP55,940 (Chang et al. 1993). *P. lividus* produces anandamide and exhibits FAAH activity (Bisogno et al. 1997). *M. edulis* specifically binds $[^3H]$anandamide (Stefano, Liu, and Goligorsky 1996), produces anandamide (Sepe et al. 1998), and exhibits FAAH activity (Stefano et al. 1998). *H. medicinalis* binds $[^3H]$anandamide (Stefano, Salzet, and Salzet 1997) and produces

anandamide (Matias et al. 2001). *T. tessulatum* binds [^{3}H]anandamide (Stefano, Salzet, and Salzet 1997).

Conversely, some non-molecular studies imply an absence of CB receptors in non-vertebrates: Brains dissected from *A. mellifera* showed show no specific binding of [^{3}H]CP55,940 and [^{3}H]SR141716A, showed no activation of GTP γS by Δ^9-THC or the synthetic CB ligand HU210, and contained no measurable levels of anandamide (McPartland, Mercer, and Glass 2000). Heads and bodies of *D. melanogaster* did not bind [^{3}H]CP55,940 and [^{3}H]SR141716A, contained little or no anandamide, and did not express FAAH (McPartland et al. 2001). A panel of insects including *G. marginatus*, *S. frugiperda*, and *Z. atratus* showed no specific binding to [^{3}H]CP55,940 and [^{3}H]SR141716A (McPartland et al., 2001c). The organisms included in this supplemental data will be integrated into the CB gene tree, placed in positions determined by an aligned phylogenetic tree. The phylogenetic tree is based on current taxonomic models ("The Tree of Life," <http://ag.arizona.edu/tree>; Aguinaldo et al. 1997; Adoutte et al. 2000), and is designed to mirror the CB gene tree, to aid in its interpretation. The CB gene tree and the phylogenetic tree cannot perfectly match, however. Incongruencies between single-gene trees and phylogenetic trees arise because of gene duplications, gene lineage sorting (deep coalescence), or HGT (Maddison 1997).

Investigation of HGT

CNR1 and *CNR2* sequences were compared with all cDNA sequences of *C. sativa* deposited at GenBank™, and the entire genome of *A. thaliana* (Arabidopsis Genome Initiative 2000), as well as a non-redundant search of all prokaryotic (Archaea and Bacteria) sequences deposited at GenBank™. A search of fungal cDNA sequences, including the entire genome of *Saccharomyces cerevisiae*, was completed previously (McPartland, Mercer, and Glass 2000), and selected fungi were subjected to radioligand binding studies (McPartland and Glass 2002). Lastly, the human genome sequence was searched for degenerate CB genes (http://genome.ucsc.edu, http://www.ensembl.org), because degenerative mutations are often the fate of duplicate genes (Lynch and Conery 2000). Sequences were aligned with BLAST, as described previously.

VR vs. CB Receptors

The deduced amino acid sequences of human VR receptor genes were obtained from GenBank™, with the following accession (g.i.)

numbers: humanVR1, 9055378; rat VR1, 7513930; human VRL-1, 7706765; rat VRL-1, 8394535; mouse VRL-1, 7106445, human VRL-2, 10187954; human VR-OAC, 11055990; rat VR-OAC, 11055318; mouse VR-OAC, 11055320; rat SIC, 5263196; human ECaC, 9789941; rat ECaC, 9186904; human CaT1, 11935057; rat CaT1, 5712756. Sequences were aligned with BLAST, as described previously. A gene tree of 14 VR homologs was assembled, its branching pattern based on the percentage sequence identity measured between human VR1 and its paralogs and orthologs (Feng and Doolittle 1996). The relative ages of the VR tree and CB tree are estimated, by quantifying their respective divergences. This method is based on the neutrality theory of molecular evolution, which predicts that the rate of genetic divergence will be constant across time (and across lineages), yielding a stochastic "molecular clock" for the timing of evolutionary events (Kimura 1986).

RESULTS

CB Receptor Phylogeny

A list of *CNR1* homologs is presented in Table 1, ranked by their percentage identity to the *CNR1* sequence, as measured by BLAST 2.0. The *CNR1* orthologs from 60 other vertebrates are also deposited at GenBank™, but most of these are gene fragments. Orthologs of *CNR2* have been relatively ignored; Genbank™ contained only two: rat CB_2 gene (sharing 81% identity with human *CNR2*), and mouse CB_2 gene (sharing 82% identity with *CNR2*). The rat and mouse CB_2 sequences share 93% identity with each other; rat and mouse CB_1 sequences share 97% identity.

A CB gene tree, based on the percentage sequence identity between *CNR1* and its homologs is presented in Figure 3. Vertebrates are over-represented in the CB gene tree, coupled with a dearth of non-vertebrate gene sequences. Consequently the gene tree was supported with supplemental data that strongly implies the presence or absence of CB receptors in 13 other organisms. Their placement in the CB gene tree was guided by a juxtaposed "Tree of Life."

The CB gene tree is rooted in an ancestral CB gene. The first bifurcation of the tree represents the deep divergence between the *CNR1* and *CNR2* sequences, which share only 47% identity with each other, as measured by BLAST. This gene duplication event gave rise to separate paralogous lineages, the *CNR1* orthologs and *CNR2* orthologs. After

TABLE 1. Homologues of human CB_1 receptors, with percent identity calculated with BLAST 2.0 algorithm.

Species	Percent identity with human CB_1 gene sequence
Monkey (*Macaca mulatta*) CB_1	100% of 472 amino acids
Rat (*Rattus norvegicus*) CB_1	97% of 473 amino acids
Mouse (*Mus musculus*) CB_1	97% of 473 amino acids
Finch (*Taeniopygia guttata*) CB_1	91% of 473 amino acids
Newt (*Taricha granulosa*) CB_1	83% of 473 amino acids
Puffer fish (*Fugu rubripes*) CB_1A	72% of 468 amino acids
Puffer fish (*Fugu rubripes*) $CB_1$1B	59% of 470 amino acids
Leech (*Hirudo medicinalis*)	58% of 153 amino acids
Human CB_2	47% of 360 amino acids

the divergence of *CNR1* and *CNR2*, a second gene duplication event gave rise to the puffer fish paralogs, CB_1A and CB_1B. A BLAST search of the human genome did not identify any degenerate CB receptor paralogs (psueudogenes) in *Homo sapiens*, suggesting that a similar gene duplication did not occur in humans, or the duplicate gene in humans subsequently mutated beyond recognition.

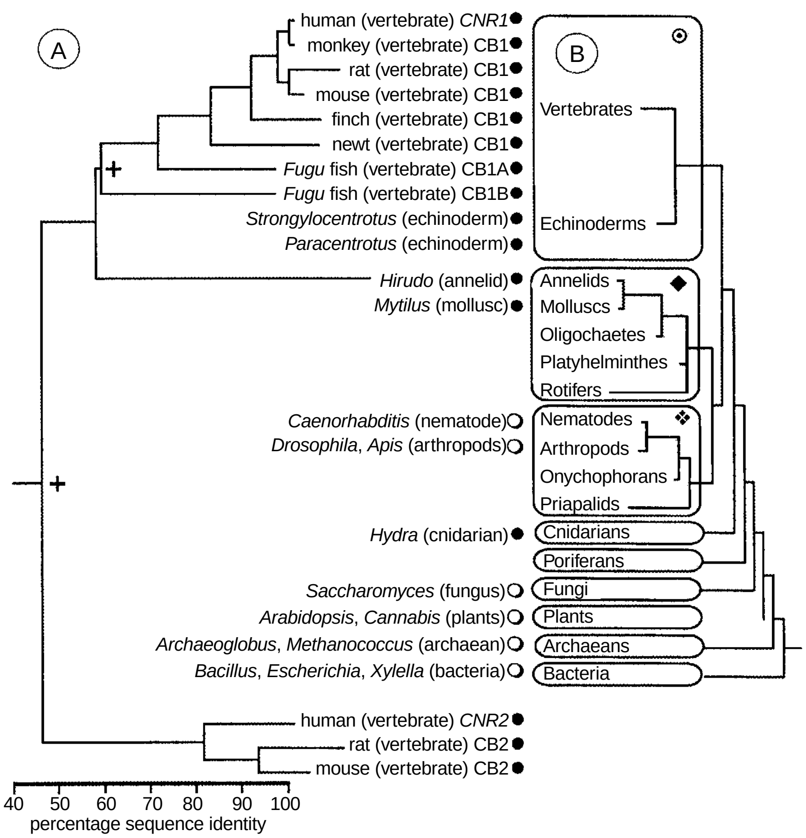
Searching for Evidence of HGT

Screening all cDNA sequences of *C. sativa* deposited at GenBank™, as well as the entire genome of *A. thaliana*, did not reveal any orthologs of human CB receptors. The *A. thaliana* sequence with best BLAST alignment, Mre11 protein (g.i. 5524769), exhibited only 28% identity, over a stretch of 83 amino acids (a mere 18% of the *CNR1* sequence). A non-redundant search of all Archaea and Bacteria sequences deposited at GenBank™ did not disclose any gene products with significant identity to human CB genes.

VR Receptor Phylogeny

BLAST aligned human VR1 and a rat ortholog, sharing 85% identity. The SIC sequence was closely related, sharing 82% identity with VR1. The clade of VR-OAC receptors collectively shared 50% identity

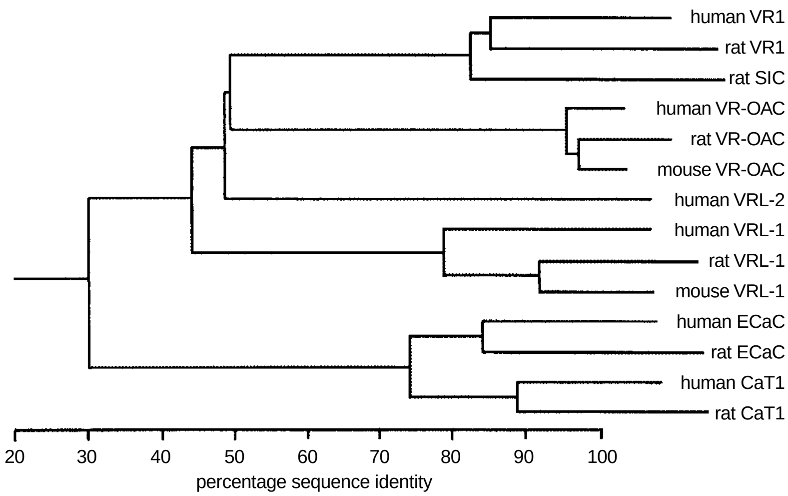
FIGURE 3. The CB receptor gene tree with supplemental data (A), mirrored by a phylogenetic tree of major taxonomic clades (B).



A. CB recptor gene tree, based on similaritiese between 12 cloned seqeuences; supplemental data includes 15 other organisms with evidence suggesting they express CB recptors (●) or they do not (❍).
B. Phylogenetic tree of life, emphasizing the Deuterostomes (⊙, which are over-represented in the mirrored gene tree), the Lophotrochozans (◆), and the Ecdysozoans (❖). Gene duplications events are marked (+).

with VR1; within the clade, rat VR-OAC shared 97% with the mouse ortholog and 95% with the human ortholog. VRL-2 shared more identity with VR1 (49%) then did the VRL-1 clade (collectively about 42% identical to VR1). Within the VR-1 clade, rat shared 92% with mouse and 79% with human. The greatest divergence was seen in with ECaC and CaT1, both clades shared 30% identity with VR1. The ECaC clade and the CaT1 clade shared 73% identity with each other. The ECaC

FIGURE 4. The VR receptor gene tree, based on similarities between 14 cloned sequences



orthologs were 83% identical and the CaT1 orthologs were 89% identical. The similarity between these sequences and VR1 was used to construct a VR gene tree, illustrated in Figure 4. The VR gene family exhibits deeper divergences than the CB gene tree, at several levels.

DISCUSSION

CB Receptor Phylogenetics

The CB gene tree (Figure 3) suggests an ancient CB gene underwent a duplication event, giving rise to present-day *CNR1* and *CNR2*. The duplication event must have occurred prior to the divergence of vertebrates and invertebrates, because at least one product of the duplication, the CB_1 gene, has orthologs in both vertebrates (fish, amphibians, birds, mammals) and invertebrates (leech). The divergence between *CNR1* and *CNR2* (47% identity) is greater than that between *CNR1* and the leech CB_1 gene (58% identity), suggesting the duplication event is older than the leech CB_1 gene. The study of CB_2 genes in other animals needs further attention. The antiquity of the duplication event is supported by the wide separation of *CNR1* and *CNR2* in the human genome, on chromosomes 6q14-15 and 1p35-36, respectively.

The *CNR1-CNR2* sequence divergence corresponds to a dissimilarity in physiology. Whereas CB_1 receptors are primarily expressed by cells in the central nervous system, CB_2 receptors are located in immune cells (B-cells, monocytes, T-cells, etc.) and immune tissues (tonsils, spleen, etc.). This ramification enables the cannabinoid signaling system to span the psycho-neuro-immune axis (aka, "the mind-body connection"). CB_1 and CB_2 have also diverged in their pharmacology. CB_1, for instance, binds anandamide with four-fold greater affinity than does CB_2; CB_2 binds Δ^9-THC with 16-fold greater affinity than does CB_1 (reviewed by Felder and Glass 1998). Some synthetic cannabinoids bind to CB_1, with nearly no affinity for CB_2, on the order of 1000-fold selectivity (Di Marzo et al. 2001).

Because CB receptors are present in vertebrates as well as very primitive metazoans (*Hydra vulgaris*), the CB gene must have evolved prior to the divergence of these organisms' ancestors, which happened at least 600 million years ago (Lee 1999). This dates to the earliest multicellular animals, which were experiencing a rapid evolutionary burst in concert with their new needs for cell-to-cell communications. Phylogenetic studies indicate many neuroreceptor GPCRs appeared during this evolutionary horizon, in parallel with the "Cambrian explosion" of metazoan animals documented in the fossil record (Peroutka and Howell 1994; Xue 1998).

Yet, Figure 3 illustrates a lack of CB receptors in some animals. The paucity of data concerning non-vertebrates makes it difficult to discern the broader taxonomic boundaries between the "haves and the have-nots." Salzet et al. (2000) concluded that CB receptors are conserved in animals from Cnidarians (*Hydra*) to humans (*Homo*). Elphick and Egertová (2001) concluded that CB receptors evolved after Deuterostomes (e.g., vertebrates and echinoderms) diverged from Protostomes (annelids, molluscs, nematodes, insects, cnidarians, and poriferans). Their conclusion required the rejection of many previous studies: Elphick (1998) dismissed the leech CB_1 gene, characterizing it as a primordial CB/melanocortin hybrid, and not a functional CB_1 receptor. The CB gene tree (Figure 3) disputes his hypothesis, because the leech gene evolved *after* the divergence of CB_1 and CB_2 genes, so it cannot be a primordial predecessor. The leech sequence clearly segregates to the CB_1 lineage. This can be confirmed by close inspection of the leech sequence in transmembrane helix 3 (Figure 2). The leech sequence has a lysine residue at position 3.28, which is critical for CB_1 function (Song and Bonner 1996), but the sequence has substitutions at CB_2-specific

sites, such as methionine 3.34 (Chin et al. 1999), serine 3.31, and threonine 3.35 (Tao et al. 1999). The leech receptor's functionality has also been confirmed by radioligand binding studies (Stefano, Salzet, and Salzet 1997).

Subsequently, Elphick and Egertová (2001) dismissed the leech CB_1 gene as a possible artifact arising from DNA contamination. They disregarded the *H. vulgaris* binding studies by De Petrocellis et al. (1999) because the stereoselectivity of this binding site was not tested. They rejected the *M. edulis* and *H. medicinalis* binding studies (Stefano, Liu, and Goligorsky 1996; Stefano, Salzet, and Salzet 1997) as "non-standard" because they used tritiated anandamide.

Alternatively, all the aforementioned studies can be accepted. From this perspective, McPartland, Glass, and Mercer (2000) concluded that CB receptors were present in Deuterostomes and *some* Protostomes. The lack of CB receptors in insects was interpreted as a sorting event that occurred in the course of insect evolution. They hypothesized that insects secondarily lost CB receptors because of a lack of ligand; anandamide is a metabolite of arachidonic acid, and insects produce little or no arachidonic acid in their tissues, in contrast to Deuterostomes and most other invertebrates.

The addition of nematode genome data (McPartland 2001), however, permits a more elegant interpretation of the CB gene tree, based on new animal taxonomy: Aguinaldo et al. (1997) proposed that Protostomes diverged into two clades. The Lophotrochozoa (lophophore-bearing animals with trocophore larvae) include the annelids, molluscs, platyhelminthes, and rotifers. The Ecdysozoa (animals that undergo molting during their life cycle) include the nematodes, arthropods (insects and crustaceans), onychophorans, and priapalids.

Thus, Figure 2 suggests that CB receptors may be absent in the Ecdysozoa, but retained in other invertebrates (the "higher" echinoderms and lophotrochozoans, and the "lower" cnidarians). Why CB receptors were secondarily lost in a clade of molting animals is open to conjecture. The mechanism driving this sorting event may be due to phospholipid biochemistry, or due to cellular modifications associated with molting, such as the loss of locomotory ectodermal cilia. Indeed, a recent study of β-thymosin orthologs (Manuel et al. 2000) demonstrated that the conserved version of these actin-binding polypeptides was absent in Ecdysozoan organisms (*D. melanogaster* and *C. elegans*), but present in bookend clades, including the Deuterostomes (sea ur-

chins and vertebrates), Lophotrochozoans (leeches and mussels), and the lower Poriferans (sponges).

A few reports in the literature conflict with the Ecdysozoa hypothesis. Egertová, Cravatt, and Elphick (1998) reported 5% specific binding of [^{3}H]CP55,940 in muscles of the locust, *Schistocerca gregaria*, but they questioned their own findings. Howlett et al. (2000) detected specific binding of [^{3}H]CP55,940 in *D. melanogaster* heads, but the binding was not displaced by CB_1-specific SR141716A or CB_2-specific SR144528. Previously, Howelett et al. (1990) reported no binding of [^{3}H]CP55,940 in a mollusc (*Aplysia californica*) and a vertebrate (a lamprey reported as *Ichthyomyzon intercostus* but probably *I. unicuspis*).

The literature contains another level of non-molecular evidence that we did not include in the supplemental data, that of pharmacological studies. Many researchers have reported changes in organisms after giving them Δ^9-THC; sometimes this data is used to infer the presence of CB receptors in the affected organisms. This inference may not be true, because Δ^9-THC causes many non-receptor effects (reviewed by McPartland and Russo 2001). Hence, pharmacological studies can only hint at the presence of receptors.

For instance, pharmacological studies have demonstrated that Δ^9-THC is antifungal; it inhibited the growth of *S. cerevisiae* (El Sohly et al. 1982) and *Phomopsis ganjae* (McPartland 1984). But *P. ganjae* shows no specific binding with [^{3}H]CP55,940 and [^{3}H]SR141716A, and BLASTing the entire genome of *S. cerevisiae* found no CB gene orthologs (McPartland and Glass 2001). Accordingly, the antifungal effects of Δ^9-THC are not mediated by CB receptors (the mechanism may be Δ^9-THC stimulation of phospholipase A_2 or inhibition of cytochrome P_{450} enzymes, both of which are non-CB receptor effects).

Some pharmacological studies contradict other lines of evidence. Acosta-Urquidi and Chase (1975) exposed *A. californica* to Δ^9-THC, which produced a change in the slug's nerve action potentials. This hints at a CB receptor-mediated effect, and it agrees with DiMarzo et al. (1999) who detected 2-AG and FAAH-like activity in *Aplysia*, but it conflicts with the negative binding studies reported by Howlett et al. (1990).

Two pharmacological studies are particularly evocative in their support of the Ecdysozoa hypothesis: Rothschild and Fairbairn (1980) demonstrated behavioral changes in moths (*Pieris brassicae*) exposed to Δ^9-THC. Nearly identical behavior, however, was aroused by cannabidiol (CBD), a ligand with little affinity for CB receptors. This sug-

gests that the behavioral changes were not mediated by CB receptors. Nevertheless, Δ^9-THC and CBD must activate moth olfactory receptors. Waser (1999) fed [^{3}H]Δ^9-THC to ants (*Formica pratensis*); their brain tissues accumulated the tritiated material, but the ants showed no significant changes in behavior. In contrast, ants fed [^{3}H]LSD were severely altered; this is because [^{3}H]LSD binds to well-known serotonin and dopamine receptors in insect brains (Blenau, May, and Erber 1995).

The Ecdysozoa hypothesis requires further testing. The best evidence for these experiments would be genetic cloning studies. Radioligand binding studies are subject to false negative results if receptor levels are low, especially against a high noise background (i.e., high levels of non-specific binding). When radioligand studies are positive, however, they have fine predictive value for the presence of CB receptors. The same cannot be said for the extraction of endocannabinoids from animals. McPartland et al. (2001) extracted 2-AG from neural tissues of *A. mellifera* and *D. melanogaster*, even though overwhelming evidence suggests these organisms lack CB receptors! This conundrum was clarified by Hoyle (1999), who demonstrated that there is greater evolutionary pressure to conserve receptor ligands than to conserve the neuroreceptors themselves. Endocannabinoids in insects may protect them from predators who *do* have CB receptors. The defense glands of an aquatic beetle, *Agabus affinis*, were recently shown to contain 2-AG (Schaaf and Dettner 2000). These glands discharge when the beetle is seized by a fish. In a feeding assay with minnows (*Phoxinus phoxinus*), spiking pellets with 100 µg of 2-AG deterred pellet consumption (Schaaf and Dettner 2000). Similarly, parasitic Ecdysozoans may secrete 2-AG in order to blunt the immune reactions of their hosts. In these cases, the presence of endocannabinoids may be a case of convergent evolution, homoplasy rather than homology.

Searching for Evidence of HGT

Our inability to find CB homologs among *C. sativa* genes is not surprising, because little of this plant's genome has been deposited at GenBank™. The absence of CB homologs in the entire genome of *A. thaliana*, however, is telling. Although the genera *Cannabis* and *Arabidopsis* belong to different plant families, evidence suggests that the Plant Kingdom displays considerable synteny (conservation of gene order). All of the deposited *C. sativa* genes have orthologs in the *A. thaliana* genome (pairwise BLAST searches, data not shown). The gene encoding

Δ^9-THC synthesis (when it is found), may also have an ortholog in the *A. thaliana* genome; *A. thaliana* has genes that code for the production of alkaloids and phytoalexins that *A. thaliana* is not known to synthesize (Arabidopsis Genome Initiative 2000). The *A. thaliana* genome is full of surprises, including genes obtained from bacteria via HGT, and the orthologs of dozens of human disease genes, such as Niemann-Pick, Wilson, breast cancer, cystic fibrosis, and hyperinsulinism (Arabidopsis Genome Initiative 2000). None of these human orthologs, however, codes for a GPCR protein. Only 27 *A. thaliana* genes code for proteins that resemble GPCRs (Arabidopsis Genome Initiative 2000), so the lack of CB gene orthologs in *A. thaliana* is reasonable.

GPCRs are similarly rare in Prokaryote genomes, so we should not be surprised by the lack of CB homologs in these potential HGT gene vectors. Fungi, however, may code for dozens of GPCRs, and the ligands signaling these receptors have yet to be identified (Bölker 1998). A previous study, however, determined that none of the GPCR-related genes in *Saccharomyces cerevisiae* code for CB orthologs (McPartland and Glass 2001). Tritiated cannabinoid ligand binding studies on a panel of fungi were also negative. Taken together, these results suggest that CB receptors evolved in primitive animals, and did not radiate via HGT from fungi, plants, or prokaryotes.

Anandamide as a Ligand for VR Receptors vs. CB Receptors

Comparing the CB gene tree (Figure 3) with the VR gene tree (Figure 4) illustrates deeper divergences in the latter. For example, human and rat orthologs of CB_1 share 97% identity, whereas human and rat orthologs of VR1 share only 85% identity. The VR gene tree has diverged into six major branches, while the CB gene tree has only two: CB_1 and CB_2. The lowest branch of the CB tree has 47% similarity, whereas the lowest branch of the VR tree has 30% similarity, again indicative of deeper divergence. The deeper sequence divergences reflect deeper physiological divergences. CB_1 and CB_2 still recognize each other's ligands (although their relative affinities have diverged), whereas the VR homologs have widely diverged in their gating mechanisms.

Since the degree of divergence is correlated with evolutionary time, this analysis suggests the primordial VR receptor predated the primordial CB receptor. We therefore infer that anandamide originally evolved as the ligand of the older receptor. This analysis is speculative, because it is based on two assumptions. First, it is based on the neutrality theory

of molecular evolution, which predicts that the rate of genetic divergence will be constant across time and different species (Kimura 1986). Neutrality theory, like HGT theory, is at odds with orthodox Darwinians, who maintain that evolutionary change at the molecular level is due entirely to natural selection. Our second assumption is that CB genes and VR genes evolved at similar rates. In other words, they pass a "relative-rate" test used to calibrate the molecular clock (International Human Genome Sequencing Consortium 2001).

Our proposal that anandamide originally evolved as a VR1 agonist agrees with data reported by Szallasi and DiMarzo (2000), who noted that regions of the brain with high levels of anandamide correlate with the regional expression of VR1. To wit, some anandamide-rich areas, such as the brainstem, have correspondingly few CB_1 receptors (Szallasi and DiMarzo 2000), suggesting that the primary target of anandamide in these regions may be VR1 receptors (Di Marzo et al. 2000).

From another perspective, Sugiura et al. (1999) also argued that CB_1 was not the original receptor for anandamide. Instead, they presented evidence that CB_1 was originally a 2-AG receptor, based on binding studies and ligand extraction studies. Gonsiorek et al. (2000) presented similar data for CB_2.

Arguments contrary to our proposal focus on the fact that anandamide has less affinity for VR1 than it does for CB_1 (Smart et al. 2000). We interpret this as evidence that the receptors are continuing to evolve. VR1 may be evolving away from the ligand and towards a temperature-gated mechanism. Indeed, a splice variant of VR1 was recently described (Schumacher et al. 2000), and it completely lost its ability to bind capsaicin. Splice variants are alternative ways in which a gene's protein-coding sections (exons) are joined together to create a messenger RNA molecule and its translated protein.

CB genes also continue to evolve. Shire et al. (1995) described a *CNR1* splice variant. Tsai, Wang, and Hong (2000) described a *CNR1* microsatellite polymorphism. Microsatellites are mutated DNA loci that contain nucleotide repeats; the CB_1 microsatellite is an AAT triplet repeat. Gadzicki, Muller-Vahl, and Stuhrmann (1999) described a CB gene with a single nucleotide polymorphism (SNP, pronounced "snip"). A SNP is a point mutation in the DNA sequence. There are a lot of them. The SNP Consortium (http://snp.cshl.org), has identified 1.42 million SNPs in the human genome (International Human Genome Sequencing Consortium 2001), including over a dozen SNPs of *CNR1* and *CNR2*.

Concluding Remarks

Gene duplication events, splice variants, and SNPs are the most common mechanisms generating the evolution of new genes (Lynch and Conery 2000). Results presented in this paper suggest these mechanisms, and not HGT, generated the genes for CB receptors.

The CB gene tree traces the origin of CB receptors back at least 600 million years. The primordial CB gene probably diverged from a closely-related GPCR, such as EDG-1. These GPCRs are gated by ligands derived from fatty acids. They evolved from older GPCRs gated by biogenic amines, which first appeared when plants and animals diverged, about 1200 million years ago (Peroutka and Howell 1994). All GPCRs may be predated, however, by the ionotropic glutamate receptor (iGluR) (Chiu et al. 1999). The iGluRs are ligand-gated ion channels, related to VR1. VR1 belongs to the TRP family of ion channels, whose ancestors can be found in *D. melanogaster* and *C. elegans*, and some of these receptors are activated by arachidonic acid, the precursor of anandamide (Harteneck, Plant, and Schultz 2000).

Unlike the evolutionary fate awaiting most new genes, the primordial CB gene survived. Our results suggest the CB gene survived because it linked with a pre-existing VR1 ligand, anandamide. Duplicate receptors are powerful sources of biological novelty, because the second receptor is not under constraints to maintain its original ligand and can accept mutations (Baker 1997). The primorial CB receptor, lacking selective constraints, eventually acquired a mutation that coupled it with 2-AG. This new receptor-ligand couplet gained novel functions, which apparently were advantageous. New receptors activated by new ligands often become fixed and stabilized by the selective forces of evolution (Goh et al. 2000). Nevertheless, one clade of animals, the Ecdysozoans, has secondarily lost the genes coding CB receptors. Investigating the physiology of these animals lacking an endocannabinoid system will shed light on this system's role in our own physiology.

Finally, a better understanding of CB and VR receptors may enable us to combine the beneficial effects of *Cannabis* spp. and *Capsicum* spp. The synthetic CB-VR "hybrid" ligand, arvanil, has excellent therapeutic potential as an analgesic, a vasodilator, and as a potent antiproliferative agent against human breast cancer and prostate cancer (Di Marzo et al. 2001). It is intriguing to regard whole cannabis as a CB-VR "hybrid," because the plant contains eugenol and guaiacol (McPartland and Russo 2001). Eugenol and guaiacol are capsaicin congeners used as dental analgesics, and they may activate VR1 re-

ceptors (Ohkubo and Shibata 1997). We need to elucidate the close association of these compounds and their multiplicity of neuroreceptor targets. The endocannabinoid system, like the "high" it can engender, is not a linear business.

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BOOK REVIEWS

CANNABIS UND CANNABINOIDE. PHARMAKOLOGIE, TOXIKOLOGIE UND THERAPEUTISCHES POTENTIAL. Grotenhermen, F. (Hrsg.). *2001. Bern, Germany:Huber, 469 pp., DM 68, Euro 34.77, softcover.*

CANNABIS AND CANNABINOIDS. PHARMACOLOGY, TOXICOLOGY, AND THERAPEUTIC POTENTIAL. Grotenhermen, F., and E. Russo (Eds.). *2002. Binghamton, NY: The Haworth Press, Inc.: in press.*

The fascinating field of cannabis and cannabinoid research has expanded within the last few years into a wide and complex landscape. This is mainly due to the discovery of a neuromodulator/neurotransmitter system with specific cannabinoid receptors and their endogenous ligands, involved in pain perception, short term memory, immunomodulation, regulation of muscle tone, blood pressure, intraocular pressure and appetite, in reproduction and various other functions. This system has been found in mammals, fish and invertebrates down to primitive leeches and thus appears to be many millions of years old.

Insights into the natural and pathological function of this endocannabiniod system have fundamentally facilitated our understanding of the therapeutic actions of exogenous cannabinoids, as well as their possible detrimental effects. Some non-receptor mediated effects have been discovered as well, and are current subjects of laboratory and clinical investigations.

It has become impossible for a researcher to overview all the facets and aspects of cannabinoid chemistry, pharmacokinetics and pharmacodynamics, of neuropharmacology, medicinal uses and health hazards.

Every year more than 300 papers on the subject appear in international journals, bearing witness of the increasing available data and explanations on the mechanisms of action of cannabinoids.

This book [appearing in German and English editions] is overdue and timeless, bringing together experts in their areas, scientists, clinicians and practitioners with a deep understanding of the subject they present in this volume, among them Raphael Mechoulam, Roger Pertwee, Rick Musty, Nadia Solowij, Robert Clarke, Kirsten Müller-Vahl, Antonio Zuardi, and Rudolf Brenneisen, just to mention eight contributors from eight different countries.

In 38 chapters on 469 pages [German edition] we find a presentation of nearly every medical aspect of the cannabis plant and the cannabinoids, that may interest scientists and health care professionals desiring an overview on the current state of knowledge. Subjects extend from the medical use of cannabis products in ancient times, to recent research results on the endocannabinoid system, from the botany of natural cannabis as medicine to the properties of promising cannabinoid derivatives under clinical investigation, from the mechanisms of cannabinoid analgesia and of neuroprotective effects, to practical dosage advices, the management of an acute overdose and possible interactions with other medical drugs.

The editor not only succeeds in bringing together about 50 renowned experts with different backgrounds and views representing the broad knowledge of cannabinoid research, but also in creating a well-structured readable book. Franjo Grotenhermen and the contributors to this volume can be congratulated for the result of their efforts. In particular in the German language area, Grotenhermen, Chairman of the International Association for Cannabis as Medicine, is known for his pleasant matter of fact attitude towards controversial topics surrounding the pharmacological actions of the drug, with a spirit found in this book as well. I appreciate his ability to present complex issues in a clear and comprehensible way.

The thirty-eight chapters are divided into six sections, the first dealing with botany, taxonomy, chemistry and history, the second with pharmacology and pharmacokinetics, the third with indications for medical use of cannabis and THC. The fourth section examines the possible risks and side effects of cannabis, and the fifth therapeutic uses of other cannabinoids (cannabidiol, anandamide, ajulemic acid and dexanabinol). In the last section we learn about other constituents of the hemp plant with possible medical value (terpenes, flavonoids, fatty acids and others).

You may find that you do not start reading the book at the beginning, but rather leaf through it, stop at one of the many figures and illustrations, at a certain table or heading, first concentrating on a chapter of your personal interest. What is known about the use of cannabinoids in migraine treatment? What are the consequences of prenatal exposure to cannabis? What restrictions on medical use should merit attention? Four of the six sections are introduced by comprehensive reviews allowing a quick orientation on pharmacological actions of cannabinoids, therapeutic uses and main side effects.

Authors with different views on the therapeutic benefits of cannabis and with contrasting assessments of potential adverse effects receive a hearing in this book. There is a chapter on "dependency" in the section on therapeutic indications for cannabis and THC and in the section on risks and side effects. It is not surprising that Tod Mikuriya, a Californian psychiatrist and practitioner dealing with patients who use cannabis to treat mood disorders and addiction to alcohol and opiates has a different approach to cannabis and dependency as compared to Wayne Hall, Head of the National Drug and Alcohol Research Center in Sydney, who is, for example, more often confronted with recreational users who have addiction problems with heavy chronic use of marijuana. There is a chapter dealing with possible side effects on the immune system by Guy Cabral, as well as a chapter debating the possible therapeutic implications for autoimmune diseases by Robert Melamede. Other controversial issues examined in the book are the use of natural cannabis products versus single cannabinoids, long-term effects of cannabis on cognition, fertility, and the hormonal system.

This is not a mainstream book. Every reader will find statements and conclusions of some authors that will provoke disagreement. These statements reflect the preliminary status of different findings, the background of the corresponding author and his or her attitude in an area of continuous conflict called the cannabis debate. Thus, the book will not give final answers to many questions, but it allows a deep insight into the many aspects of the ongoing controversies and provides a great deal of up-to-date information on the current state of knowledge that makes it a valuable reference book.

Leslie Iversen, professor of pharmacology at Oxford University and main scientific adviser for the House of Lords inquiry of cannabis in 1998 writes in his preface: "The editors should be congratulated for

having assembled such a well balanced volume." Everything you've always wanted to know about cannabis (but were afraid to ask), you get to know in this book. This book is an absolute must.

Ulrike Hagenbach, MD
REHAB Basel
Zentrum für Querschnittgelähmte und Hirnverletzte
Im Burgfelderhof 40
CH-4055 Basel
Switzerland
E-mail: u.hagenbach@rehab.ch

ADVANCES IN HEMP RESEARCH. Ranalli, Paolo (editor). *Binghamton, NY: Food Products Press, 1998, 266 p., $99.95, hardcover.*

This book represents a true international collaboration of authorities presenting the latest information on culture and processing of cannabis. Although primarily geared toward industrial hemp and its applications, this volume also presents interesting information on the botany of cannabis, its phytochemistry, and methods for detecting and monitoring plant THC content, which is a necessary element for any cultivation program due to national and international regulations.

David Pate's chapter on hemp seed as a food resource is a particular standout with therapeutic implications, representing one of the few accessible scientific analyses of the dietary implications of linolenic, linolenic, and gamma linolenic acids in health and disease.

This book would be essential reading for any commercial or research cultivator of cannabis.

Ethan Russo, MD

WAITING TO INHALE: THE POLITICS OF MEDICAL MARIJUANA. Bock, Alan. *Santa Ana, CA: Seven Locks Press, 2000, 285 p., $18.95, softcover.*

Alan Bock is a senior editorial writer for the *Orange County Register*. He has stepped aside from those duties long enough to document the modern history (especially 1996-present) of clinical cannabis in the USA, with a particular focus on California, arguably the epicenter of its political development.

This book is a well-conceived and readable chronology of events that examines the topic from both sides of the issue. A refreshing number of direct quotations and testimony provide the reader with the feeling of "being there," and taking part in the unfolding history. While decidedly "pro" on the issue of clinical cannabis, the arguments of the government, and the applicable laws, are examined in fine detail. Thus, the positive opinion is a studied one that is amply justified in the text.

Any historian or sociologist examining the history of this topic will find this book indispensable. Similarly, the author tackles the medical and legal issues in a manner that is approachable for readers who lack the corresponding professional backgrounds.

This book is a worthy successor and complement to the earlier medical histories of Musto, legal analyses of Bonnie and Whitebread, and period pieces of Sloman.

Ethan Russo, MD

HEMP DISEASES AND PESTS: MANAGEMENT AND BIOLOGICAL CONTROL. McPartland, J. M., R. C. Clarke, and D. P. Watson. *Wallingford, UK: CABI Publishing, 2000, 251 p., $100, hardcover.*

It is infrequently the case that a book can be labeled as definitive or authoritative, but these are appropriate terms describing this volume and its treatment of the subject matter. It manages a difficult task by being simultaneously comprehensive, scientifically sound, visually striking, and entertaining to read. The informative text is supplemented by astonishing photographs of the myriad organisms that infest, parasitize or feed upon the cannabis plant. It is frequently stated in the lay litera-

ture that hemp is "pest-free," but this is only a relative statement. *Hemp Diseases and Pests* illustrates this fact in a convincing fashion in its treatment of the insect, bacterial, viral, fungal and animal species that act as cannabis predators.

The necessarily academic tone is nicely punctuated by disarming humor: One table of cannabis insects is captioned, "Bugs-the good, the bad, and the ugly (all x6)." It is to the publisher's credit that such examples were retained in the final version.

The book is also refreshing for its completeness. It is not content to merely describe each cannabis affliction, but rather, proceeds to examine its ecological role and remedies by chemical, beneficial bug, or rational organic methods. The latter are emphasized as preferred methods for cannabis culture designed for human consumption. A dichotomous key of diseases and pests is sufficiently useful to justify the price of the book on its own merit.

From a therapeutic standpoint, important information is highlighted with regard to the control of fungal pathogens representing a danger to immunosuppressed clinical cannabis patients, both before and after harvest.

This book should be considered essential for any individual or institution engaged in research on the cannabis plant and its culture.

Ethan Russo, MD

MOM'S MARIJUANA: INSIGHTS ABOUT LIVING. Shapiro, Dan. *New York: Harmony Books, 237 p., $20, hardcover.*

This book is a little gem. Dr. Shapiro is a clinical psychologist and faculty member at the University of Arizona in Tucson. The fact that he survived to achieve this position is the story portrayed in the narrative, which documents a personal battle of many years against Hodgkin's disease, including two separate and harrowing bone marrow transplantation procedures.

More particularly, this is the story of love and faith, between a young man, his wife and family, and the role of cannabis in assisting his survival. That story is told with gripping drama, ironic humor, and passion. It is a stirring testimony to the power of the human spirit that provides

lessons to us all. This is the medical marijuana controversy with a human face, which transcends the pre-conceived notions, biases and politics to force a view of a frequently grim reality.

This story would make a terrific movie, and were it to be cast with Tom Hanks as Shapiro, and Renée Zellweger as his spouse, I daresay that the current American War on Drugs, or at least the battle of clinical cannabis, would be over within months.

Ethan Russo, MD

EDITORIAL

This issue of *Journal of Cannabis Therapeutics* might well be labeled the European-Canadian Special Edition. That is appropriate, in view of the radical changes underway in political policies with respect to cannabis therapeutics in those nations.

Our first article is from Jörg Fachner, and illustrates original research on the effects of cannabis upon brain electrical activity (BEAM or "brainmapping"). Interesting insights are obtained.

The second is an interview with Willem Scholten and Myra Klee, two officers in the Office of Medicinal Cannabis in the Netherlands. They were kind enough to allow the editor a prolonged interview concerning Dutch policy in this area. Minor editing took place to improve the flow of the language and remove extraneous material, but no substantive changes were made in the contents. The pace of change in Europe is so fast that a recent development in Holland must be mentioned. The Dutch government has announced (October 2001) that clinical cannabis research will continue, but during the interval before it is completed, quality-controlled cannabis will soon be available by prescription in pharmacies in that country.

The next article by James Butrica reviews ancient data on cannabis from the Greeks and Romans. It has been almost 30 years since the last in-depth treatise of this type, and new insights are apparent.

Another entry comes to us from the UK, where Vivienne Crawford spins a lively tale of a *homelie herbe*, none other than cannabis, and its medical usage from the Anglo-Saxon era up to the 19th century.

Finally, we publish here a few of the many presentations available at the International Association for Cannabis as Medicine (IACM) Conference re-

cently held in Berlin, Germany. I believe the reader will be impressed with the range and quality of clinical cannabis research taking place on the Continent.

Our last entry in 2002 will be a special thematic double issue, "Women and Cannabis."

Ethan Russo, MD
Editor

Topographic EEG Changes Accompanying Cannabis-Induced Alteration of Music Perception– Cannabis as a Hearing Aid?

Jörg Fachner

ABSTRACT. An explorative study on cannabis and music perception is presented, conducted in a qualitative and quantitative way in a habituated setting. EEG-brainmapping data (4 subjects; rest–pre/post listening; 28 EEG traces; smoked cannabis containing 20 mg delta-9-THC with tobacco) were averaged and analyzed with a T-Test and a visual topographic schedule. Compared to pre-THC-rest and pre-THC-music, the post-THC-music EEG showed a rise of alpha percentage and power in parietal cortex on four subjects, while other frequencies decreased in power. Comparing pre/post music EEGs, differences ($p < 0.025$) were also found in the right fronto-temporal cortex on theta, and on alpha in left occipital cortex. Results represent an inter-individual constant EEG correlate of altered music perception, hyperfocusing on the musical time-space and cannabis-induced changes on perception of musical acoustics. Cannabis might be of help for hearing impaired persons. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

Jörg Fachner, MD, MEd, is affiliated with the Qualitative Research in Medicine, and the Institute of Music Therapy at the Faculty for Medicine of University Witten/Herdecke, 58448 Witten, Germany.

Address correspondence to: Dr. Jörg Fachner, Institute of Music Therapy, University Witten/Herdecke, Alfred-Herrhausen-Str. 50, D-58448 Witten, Germany (E-mail: Joergf@uni-wh.de).

KEYWORDS. Music, ethnography, electroencephalography, brainmapping, EEG, significance mapping, personality, auditory perception, acoustics, hearing impaired, cannabis, medical marijuana

INTRODUCTION

In the context of pop cultural developments, drugs with euphoric, sedative and psychedelic effects have been discussed to influence life-style and artistic manners of musicians (Boyd 1992; Shapiro 1988). The effect of cannabis on auditory perception and musicians' creativity has been a crucial issue since the early days of jazz (Mezzrow 1946; Sloman 1998). However, there has been little research accomplished on cannabis and music perception.

Webster (2001) discussed one reason in an earlier issue of this *Journal*. Research is part of the social life–world and researchers are social beings with reflected societal attitudes, values or prejudices. Research on stigmatized cultural lifestyle issues, consciousness and drugs is surely not a theme to open doors to a serious scientific reputation. Research should be a neutral way to the "truth of the story," but researchers are most often part of an institution with specified goals and politics, so, research in aesthetics and culture of cannabis consumption was abandoned for a long time (Webster 2001).

One of the most prominent cannabis effects is that on auditory perception. For Lindsay Buckingham, cannabis seemed to refresh his listening abilities and a break-down of pre-conceptions (Boyd 1992, p. 201), "If you've been working on something for a few hours and you smoke a joint, it's like hearing it again for the first time." George Harrison seemed to agree (Boyd 1992, p. 206), "I think that pot definitely did something for the old ears, like suddenly I could hear more subtle things in the sound." Casual listeners also seem to be convinced that cannabis enhances auditory perception (Aldrich 1944; Tart 1971). In terms of cannabis as a medicine, this issue raises the question whether or not cannabis might be used as a hearing aid.

BACKGROUND

Cannabis and Auditory Perception

Research on musical acoustics (Risset 1978) considers four parameters: pitch, duration, loudness and timbre. Defined pitch differences form melody intervals and harmony patterns. Duration is needed to identify rhythm patterns and tone length. Loudness and timbre form certain characteristics of instruments and sound sources.

Duration: Aldrich observed a small change on the Seashore-Rhythm-Scale (Aldrich 1944) produced by cannabis, a result that was replicated with higher changes by Reed in the 1970s (Reed 1974). Music as a multi-dimensional auditory *Zeitgestalt* (Zuckerkandl 1963) appears in time. Melges explained cannabis-induced effects on time perception as a speeding up of the internal clock (Melges et al. 1970; Melges et al. 1971) that is experienced as time expansion (Tart 1971). Time expansion may temporarily allow an increased insight into the "space between the notes" (Whiteley 1997). This might help experienced individuals (Becker 1963) to perceive acoustic sound structures more effectively.

Loudness: Cannabis seemed to change metric units of auditory (intensity) perception in audiological tests (Caldwell et al. 1969; Globus et al. 1978). Caldwell reported changes on intensity thresholds. Globus suggested an intensity expansion of the auditory measuring units as responsible for the experience of an enhanced intensity perception.

Pitch: In the 1940s, Aldrich observed no changes in pitch discrimination after administering oral doses of pyrahexyl, a synthetic cannabinoid (Aldrich 1944). By choosing between two different pitches, cannabis induced dose-related preferences for higher frequencies as a function of frequency (de Souza, Karniol and Ventura 1974). Higher frequencies represent the location of sound sources and the overtone spectrum of sounds. Martz investigated frequency thresholds and reported improved thresholds at 6000 Hz after cannabis intoxication (Martz 1972). For a review on audiological tests, see Fachner (1998a) and Fachner (2001).

Timbre: Thaler, Fass and Fitzpatrick (1973) investigated speech discrimination rates after cannabis intoxication and reported significant changes on different sound levels, even with hearing-impaired subjects and similar results in a follow-up study. Subjects showed an increased speech perception rate at 10 dB SL and at 40 dB SL, even when tones were covered with noise (Thaler, Fass and Fitzpatrick 1973). Another study reported no improvements during speech perception tests (Lindenman 1980). Both results suggest alterations in cerebral processing.

Rodin reported a change of prosodic structure and a change to a "sing-song-type-pattern" of subjects' responses during his experiments (Rodin and Domino 1970). Tart observed that people "understand words of a song better" and that "quality of own voice changes" after cannabis consumption. Effects were statistically ranked as characteristic and common effects (Tart 1971, p. 75). It seems that cannabis has a stimulating effect on the perception and production of prosodic and suprasegmental parts of speech, which might have had an influence on developing certain slang, a personal sound and timbre of jazz artists (Mezzrow 1946). De Souza's change of preference styles reported

above might indicate a change of overtone recognition in frequency spectra of sound sources.

Moskowitz reported an increasing number of false alarms in a task where subjects were asked to detect a randomly occurring 1000 Hz tone embedded in noise. It seemed that cannabis was stimulating tone imagination and subjects heard tones that were not there (Moskowitz 1974). Tart's subjects also reported an intensification of auditory images (Tart 1971).

Thus, cannabis seems to enhance auditory perception throughout a temporary change in the metric frame of reference and allows a larger intensity scaling of perceived musical components. This might help experienced musicians to play more intensively during improvisations (Fachner 2000). Cannabis seems to act as a psycho-acoustic enhancer, exciter, equalizer, or attentuator, used in modern recording studios, making sounds more transparent and sound sources more distinct. Greater spatial separation of sound sources and perceptions of more subtle changes in the sound were other characteristic cannabis effects in Tart's study (Tart 1971). Baudelaire's and Tart's descriptions of synesthetic effects, weakened censorship of visual depth perception (Emrich et al. 1991) and a transition to a field-dependent style of thinking (Dinnerstein 1968), suggest intensification of individual cerebral hearing strategy. This type of learning strategy promotes hyperfocusing on acoustic space, musical time-structure, and a more effective attention on auditory information (Becker 1963; Curry 1968).

This short overview on cannabis and auditory perception, more fully explored in the author's doctoral thesis (Fachner 2001), clearly suggests that there is potential for the use of cannabis as medicine for the hearing impaired. Changes in auditory test give us reason to argue that perception of acoustic shapes and higher frequencies, spatial relationship of sound sources and even speech perception, seem to be enhanced.

Will it be possible to show this subtle change in auditory perception with an EEG brain imager, which visualizes the topographic electrophysiological changes in the brain? Do we have a chance to relate cannabis-induced auditory changes to an altered individual hearing strategy?

Cannabis, Music Perception, and Brain Imaging

Cannabis effects on human behavior and lifestyle are complex issues that cannot be easily generalized or proved in a time-locked laboratory setting. Furthermore, collection of experimental EEG data about what occurs in the brain while listening to music under the influence of cannabis seems to offer many confounding variables. Results could be affected by differing inter-individual perceptual strategies of listening to music (Aldridge 1996) as might be observed in the topographic EEG, the subjective history of drug experiences and

tolerance effects, pharmacokinetics and dynamics of the specific substance absorbed (Grinspoon 1971; Julien 1997).

Furthermore, the nature of the brain imaging method and the produced data themselves (Revonsuo 2001) show different patterns of brain activity. Hemodynamic aspects, as revealed in cerebral blood flow techniques, do not necessary correlate with electrophysiological changes.

Consciousness states are variable (Tart 1975). To believe that there is something like a "normal state of consciousness" and an "altered state" after administering a drug is a more scientific way of assuming that a comparison of quantitative data of a laboratory experiment would reveal the difference of consciousness states. "Consciousness states" end up as small slices of data, artifact-free epochs of the process in a laboratory setting. Here the timeline of the actual experience might be lost or fragmented in the process of editing comparable data-epochs and eliminating artifacts. Moreover, the testing apparatus and protocol cause behavioral discomfort with necessary cables, electrodes, blood sampling with syringes, postural restrictions, etc. Furthermore, somewhat tedious or abstract test batteries, which are felt as being not adequate to the "state you're in," double blind structures with non-verbal gesturing perceived more intensely and other behavioral context interactions make this situation different from "normal."

Critiques by social scientists on these behavioral measuring procedures have addressed the situation and process of measuring which have an impact on the quality of the data (Deegener 1978). Humanistic critiques are based on the uniqueness and contextual nature of the human experience, which is dependent on biographical time and place, and uniqueness of the situation in which subjects are involved (Rätsch 1992). Leary, therefore, emphasized the importance of set and setting in a research paradigm on psychedelic substances (Leary 1997).

Situation, Ethnography and Experience of Music

The auditory perception of musical acoustics as described above is surely not the musical experience itself. What constitutes the process of music listening as a holistic musical experience of a person?

To understand what makes a certain musical experience of one composition different from another, musicologists analyze musical content by using scores. Score analysis to explain varieties of music experience has been questioned from the stance of situated performing and listening (Small 1998; Tagg 1982). Attending a concert or listening to music on the radio, adds the contextual dimension of personal experience in an ongoing situation onto perceptual processes (Buytendijk 1967; Hall 1996). This influences intention and selection of what has been heard, selected and perceived consciously during perception.

Situationism refers to "the inseparability of action and context, the relation between the social and material conditions of action, the need to theorize the 'higher psychological functioning' in relation to situated action and the tension between the emphasis on situation and the scientific ideal of abstraction" (Costall and Leudar 1996: 101).

Research on popular music stressed semiotics of signs used in artistic context, which produce meaning for performer and audience. Thus, music becomes a mediator of cultural symbols (Tagg 1987). Therefore, several issues of identity, place and performance, musical practice and production styles, mediating experience of a certain song or classic composition in a specific listening or music production situation, are taken into account to understand the aesthetic experience (Barber-Kersovan 1991; Frith 1998).

As a consequence, we should measure music perception in the context of real world cannabis culture, because the context of listening seems to be important for the situated experience of music. This method of research accompanies the cannabis smoker in an ethnographic manner. In this perspective, the manifold meaning of the data gained is context-generated and part of the actual music experience.

Music and the EEG

Research on music and the EEG reflects the problem of inter-individually different music experiences. EEG coherence analysis showed intra-individually constant EEG-coherence profiles during music perception, but profiles spread inter-individually over the whole cortex (Petsche 1994). Music listening seems to involve many different areas, but is pragmatically believed to have a right hemispheric dominance (Kolb and Whishaw 1996; Springer and Deutsch 1987) as results in EEG research conveyed (Auzou et al. 1995; David et al. 1989; Duffy, Bartels, and Burchfiel 1981; Petsche 1994; Walker 1977). However, in a review on human brain mapping methods of music perception, Sergant insisted that there is no real evidence that music seems to be processed dominantly in the right cerebral cortex (Sergant 1996). Even dichotic listening methods, auditory evoked potentials (AEP) (David et al. 1989) or positron emission tomography (PET) scan vary in stimulus-locked localization strategies of individual perceptions. Davidson concluded that variations reflect individual perceptual differences that can be observed in the baseline measuring before administering sound bits, music fragments or words (Davidson and Hugdahl 1996). Therefore, we should look closely at structural similarities of rest and music EEG Gestalt in the visual analysis of brain images.

Cannabis and EEG

Even though it is now possible to link the mechanism of cannabis action to density of cannabinoid receptors in the brain and immune system (Joy, Wat-

son, and Benson 1999), topographic pre/post EEG studies of cannabis-induced changes are not available. Transient cannabis-induced EEG changes have been previously reported in laboratory studies. Most EEG studies that exist, however, were oriented toward finding brain damage with casual or long-term use.

Quantitative EEG measuring in the 1970s commonly used 1 or 2 electrodes attached to the right occipital or parietal areas (Hollister, Sherwood, and Cavasino 1970; Rodin, Domino, and Porzak 1970; Roth et al. 1973; Volavka et al. 1971; Volavka et al. 1973; Volavka, Fink, and C.P. 1977). Results of this research are somewhat contradictory. Hanley's quantitative EEG study, done with 8 electrodes from frontal to occipital areas, found only decreased amplitudes and percentage over the whole spectrum (Hanley, Tyrrell, and Hahn 1976). Others reported an increase in relative α-percentages (alpha) and power, a decrease in main or central frequency and a transition to theta (θ) during contemplation, as well as a decrease of relative theta- or beta (β)-percentage and power (Struve and Straumanis 1990). However, only in the work of Hess and Koukkou has music been part of the experimental setting (Hess 1973; Koukkou and Lehmann 1976; Koukkou and Lehmann 1978). Both reported results that were spread in a certain order corresponding to music over the time-course of drug action. Lukas correlated euphoria and higher alpha-index during the first 20 minutes (Lukas, Mendelson, and Benedikt 1995).

Results remind us to be aware of an inter-individual implicit order of electrophysiological signal processes during personal cannabis experiences. The psychoactive action of THC induces identifiable EEG signatures, but some frequency ranges seem to be more indicative for the quality of the actual experience.

THE EXPERIMENT

Aims

The aim of this explorative pre/post-EEG study was to examine the manner in which subjects smoked cannabis and listened to music in a habituated setting of a living room.

Cannabis induces a field-related perceptual style (Dinnerstein 1968). Most EEG laboratory studies demonstrate a lack of sensitivity to the experimental setting. To reduce the laboratory-setting bias in EEG results, the field-dependence of drug action in personal set and experimental setting has to be considered by conducting research according to a suitable paradigm (Weil 1998). The topographic changes induced by cannabis while listening to music may well be radically different in the laboratory setting as compared with one in which the subject normally listens to music.

An obvious reason to use the EEG in researching cannabis and music perception is based on the high time-related resolution of the data. We can observe synchronous electrophysiological traces of cognitive activity in the EEG (Petsche 1994). While the synchronous correlation of the EEG is its big advantage, it lacks spatial resolution of data origin. We can only observe summations of generating units below the surface of the brain. With the NeuroScience BrainImager®, source information is interpolated, and provides spatial information about the distribution of cerebral changes. Amplitude and significance mapping (Duffy 1986; Maurer 1989) can be used to identify and localize changes of cerebral areas and their function during perceptive states.

With these limitations in mind, a research project, which compares pre/post-THC-EEG changes gains topographical EEG data, gives us spatial information on the cortex distribution of cannabis-induced electrophysiological changes of neural activity. But the "map is not the landscape" (Machleidt, Gutjahr, and Mügge 1989), and so we can only conclude that the frequency changes accompany cannabis-induced alteration of music perception in this particular case. After all, EEG research has gained lots of experimental data that can be compared to similar experimental topics. To research the real world situation of auditory changes an ethnographic exploration in cannabis culture seems to be a priority. These results could be compared subsequently with laboratory data.

Methods

To ensure a minimum of laboratory-setting bias, a non-blind pilot study was conducted with a mobile bedside EEG-Brain-mapping system in the consumers' habituated setting, a living room. Four subjects (3 male/1 female) smoked a tobacco joint mixed with Nepalese hashish (hereafter phrased as "THC") and listened with closed eyes to three pieces of rock music in a comfortable armchair. EEG was recorded throughout rest and music listening periods (Figure 1).

The aim to do EEG research in a naturalistic setting with minimum limitations introduced by the researcher evokes problems in estimating the quality of the data. Results of this explorative study should be regarded as a kind of physiologically correlated ethnographic description of cannabis culture in Europe. This methodology may evoke questions that should be addressed at the outset. How can we ensure visualization of substance-related music perception during a brain imaging study in an ethnographic setting?

Closed Eyes Music listening and EEG Recording

Following Baudelaire's description of cannabis intoxication stages, this study accompanies the second contemplative stage (Solomon 1966). This ethnographic setting of cannabis consumption while listening to music, goes

FIGURE 1. Experimental Schedule

Baseline State: Pre-THC-EEG (music and rest-eyes closed)

Listening to 3 Rock music pieces (defined order)

1 minute silence/rest between the songs

30 minutes intermission

Smoking 0.3 g cannabis (20 mg THC) in tobacco joint

After 10 minutes EEG start

Altered State: Post-THC-EEG (music and rest with THC)

Listening to the same music/same measuring situation and setting

4 Subjects (3 male/1 female)

back to Chinese drug culture and Harlem Tea Pads of the '30s (Digest 1934; Jonnes 1999: 119f). Nowadays a "chill-out room" in modern rave parties has the same setting characteristics. It permits a relaxed contemplative experience of music with closed eyes in the way David described physiological types of music listeners (David, Berlin, and Klement 1983). Listening to music with closed eyes was also the method used in a music therapy approach called Guided Imagery developed in psychedelic therapy (Grof 1983; Leary 1997), wherein music and psychedelic drugs were used to stimulate the unconscious to evoke individual imagination and associations (Bonny 1975; Bonny and Pahnke 1972). EEG recording with closed eyes is a common procedure in pharmacoencephalography (Struve and Straumanis 1990).

Tobacco Joint

A guideline of research in an ethnographic field in an ethno-methodological manner is to accept and describe habits, ritualistic aspects and settings of the consumer life-world (Rätsch 1992). One of the bad habits associated with cannabis consumption in Europe is the custom of mixing hashish with tobacco in a joint. The use of tobacco in this experiment is surely a crucial aspect, because the hashish-tobacco mixture causes different pharmacokinetic and dynamic action of THC compared to smoking only herbal cannabis or hashish. Furthermore, the hashish as obtained on the black market (subjects brought their own cannabis) cannot be expected to be pure. Qualitative gas chromatography testing of the smoked substance was accomplished, and quality was estimated as "medium," with approximately 20 mg Δ^9-THC in the 0.3 gram hash ("Black Nepalese") consumed. The aim of this study was to find out whether smoking

induces changes on the EEG, not to reveal a dose-related THC action profile during music perception.

No specific inhalation technique was employed to ensure a comparable smoke uptake, because this would distract from the naturalistic experimental setting. Subjects sat in an armchair and smoked at their own customary pace. Subjects obviously attained a cannabis high, said they felt "stoned" and attributed the experienced altered state of consciousness to by the smoked joint with hashish.

Music and Subjects

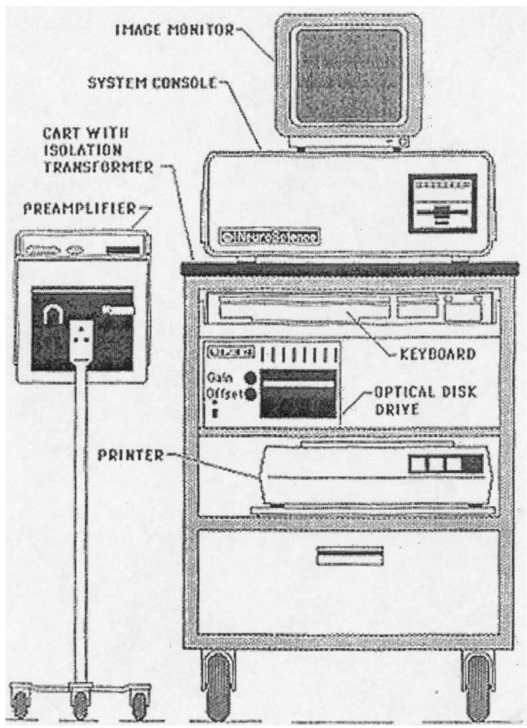
Three male subjects chosen for this explorative experiment reported themselves as experienced smokers of cannabis and tobacco. One female subject was a frequent smoker of cannabis. All of the subjects refrained from smoking cannabis previously on the day of the experiment.

None of the subjects were musicians, but regarded themselves as music lovers with a preference for alternative rock music. Musicians differ in their perception of music as EEG studies have shown (Altenmüller and Beisteiner 1996; Petsche, Pockberger, and Rappelsberger 1987). The music used in the current experiment was chosen from a single case study (Fachner, David, and Pfotenhauer 1995) with follow-up (Fachner 1998b; Fachner, David, and Pfotenhauer 1996). The first selection in the experimental sequence sounds like classical music. It is string ensemble chamber music with no vocals, drums or electric instruments, the instrumental "Prelude" by "King Crimson" (King Crimson 1974). The second, "Obsessed," is a folk-punk song with vocals, acoustic guitars, drums and bass, recorded by "Dogbowl" (Dogbowl 1989). The third piece is a live recording cover version of the Beatles' song "We Can Work It Out" performed by "King Missile" (King Missile 1989). Songs were played in the same order during pre- and post-THC conditions (Figure 2).

The NeuroScience BrainImager® samples 28 EEG traces with a 12 Bit analogue/digital converter. This produces 4096 dots per second within a dynamic range (DR) of 256 μV, providing a sample accuracy of 1/16th μV. Average maps interpolated between the 28 EEG trace sample points are processed every 2.5 seconds. The Imager is equipped with an isolation transformer and shielded pre-amplification, as well as a notch filter on 50-60 Hz to reduce the influence of electromagnetic fields in hostile environments.

Impedance levels were kept under 11 Kohms. Cut-off filters were set to 40 and 0.3 Hz. EOG (electrooculogram), ECG (electrocardiogram) or EMG (electromyography) traces for artifact control were not applied to avoid laboratory bias. Artifact control was done visually by a time-coded video protocol. After removing potential artifact maps (fronto-polar δ threshold at 105 μV on 256 μV DR), Individual (IA) and Group Averages (GA) were processed using

FIGURE 2. NeuroScience BrainImager®



- 28 Electrodes; 12 Bit A/D (4096 d/s @ 256 μV DR); Notch Filter; Cut-off: 0.3 + 40 Hz
- Average Maps over 2.5 seconds
  - Delta (0.39-3.9 Hz);
  - Theta (4.3-7.8 Hz);
  - Alpha (8.2-11.7 Hz);
  - Beta I (12.1-16.0 Hz);
  - Beta II (16.4-30.0 Hz); Spectral Map;
  - Roll-off (3 dB in 0.25 Hz)
- Individual and Group Averages Sub-Avg; Standard Deviation Mapping; T-Test (Significance Mapping)

the statistics software package of the NeuroScience BrainImager®. More details of data editing can be found in a doctoral thesis (Aldridge 2001) (Figure 3).

Pre/post rest and pre/post music listening results were averaged and subjected to a T-Test. Each piece of music and one minute of silence before the music was recorded and individually averaged. The investigation included one extended single case study with a follow-up. Research focus for each person was on individual drug and music reactions by comparing the pre/post individual averages (IndAvg) and the total group average (Gavg) of the pre/post rest and music sessions over the sample. Amplitude mapping does not provide dynamical changes of the music but represents average electrophysiological activity while listening as reflected in the maps, allowing identification of difference in the pre- and post-conditions.

RESULTS

The first illustration shows the T-Probability mapping of the EEG changes from pre- to post-THC listening for the first piece of music for one subject (Figure 4). The reference file was pre-THC listening and it was compared to post-THC music listening. From the upper left to the right we see δ-, θ-, and α-probabilities, below β I + II and the spectral mapping. The view is from above the head. What seems to be of interest for a possible cannabis-induced auditory perception style are the obvious α-changes in the left and especially in the right temporal cortex. The temporal cortex hosts the auditory system and main association areas.

While listening to the first piece of music highly significant changes ($p < 0.001$) with 3 subjects in the pre/post-comparison from pre-THC-music to the first post-THC-music average have been observed. These high significant changes after ten minutes of smoking mark the first plateau of drug action and a changed listening state. It shows that subjects experience and process music in a different way than previously. In all subjects, significance decreased with the second and third song in the sequence (Figure 5).

Upon examination of T-Test changes of the second piece of music, we can see δ-, θ- and β-changes, as well as spectral frequency speed changes on left side of brain. The left side hosts motor and sensory speech centers, which seem to change more when listening to Rock songs with words.

The map in Figure 6 shows highly significant changes from pre-THC-rest to the post-THC-music EEG of the first piece in the series. As we observed before, this T-Test again shows α-changes over the temporal regions. This might indicate changes in auditory cerebral processing. However, α-mapping showed remarkable changes in amplitude levels, as we can observe in the following illustration.

FIGURE 3. Individual (IndAvg) and Group (Gavg) Averages

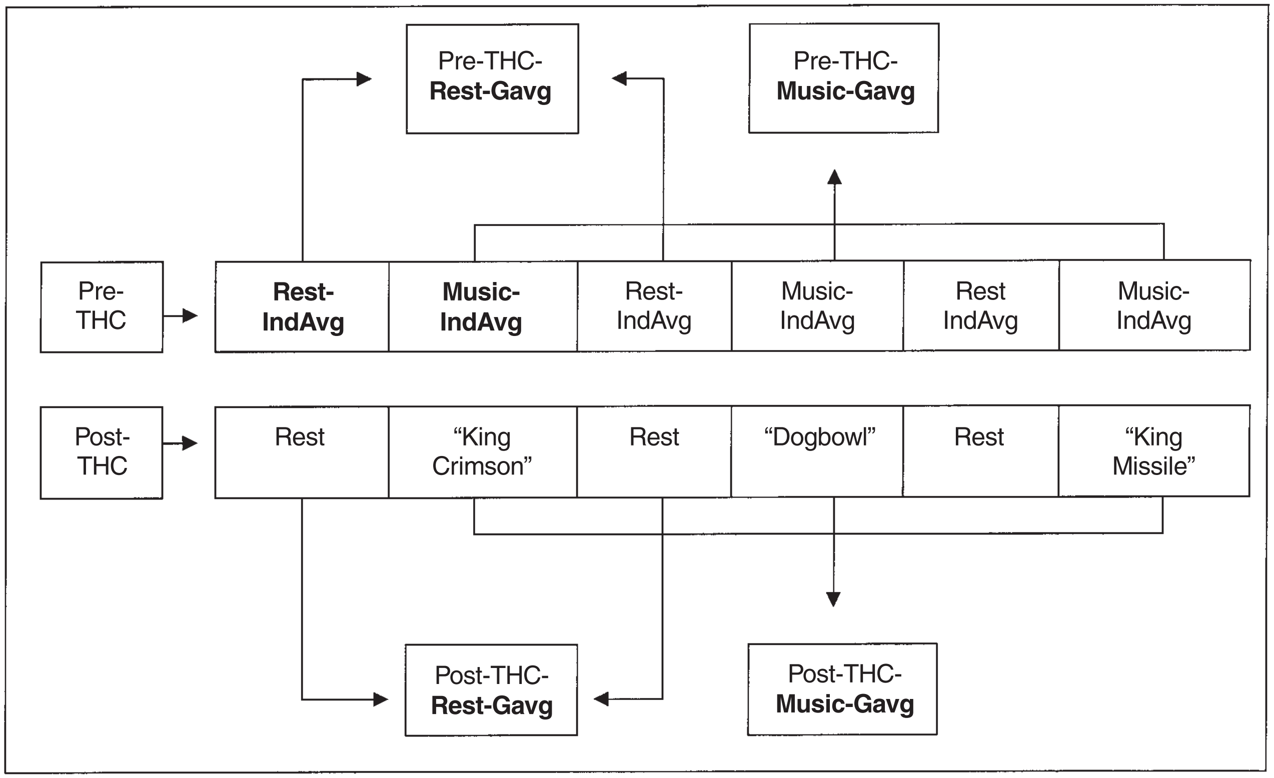


FIGURE 4. Significance Mapping T-Probabilities EEG-Changes Music

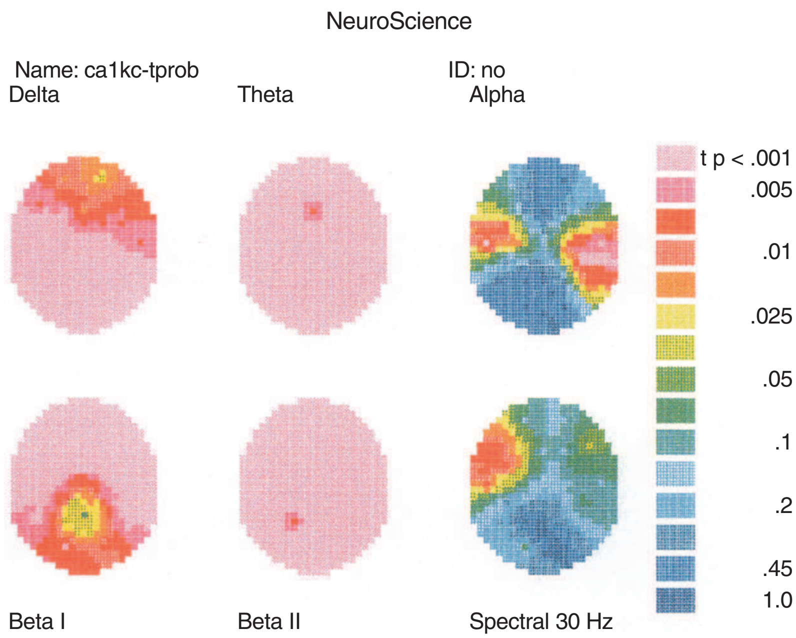


Figure 7 shows the α-GA over four subjects for the pre/post rest condition. In this figure, the 16 colors of the 30 μV Scale represent a 2-μV step on a dynamic range of 256 μV. Comparing pre/post-rest visually, a decrease of α-percentage and amplitude in the post-THC-rest-EEG was observed with all four subjects. The post-THC-rest amplitude decrease in the parietal areas showed an individual range from 6-10 μV. The GA over four subjects seen here shows a difference of 2 μV. Decrease of amplitudes in rest over the whole frequency range was reported by Hanley (Hanley, Tyrrell, and Hahn 1976) and is similarly observed in the present study.

In Figure 8 we see the pre/post α-GAs of listening to music. An increase of relative α-percentage in parietal regions was observed in the post-THC-music GA for all four subjects. Compared to the pre-THC-music EEG, the individual increase of amplitudes ranged from 2-4 μV. The α-range even indicated changes on higher and lower frequency ranges. Mapping of α-standard deviance showed highest deviance in the parietal regions.

A decrease of α-amplitudes in post-THC-rest and an increase in the post-THC-music EEG has been observed with all subjects, as well as a decrease of percentage and power of the other frequency ranges.

FIGURE 5. Significance Mapping T-Test Pre/Post Dogbowl, Second Piece of Music in the Sequence

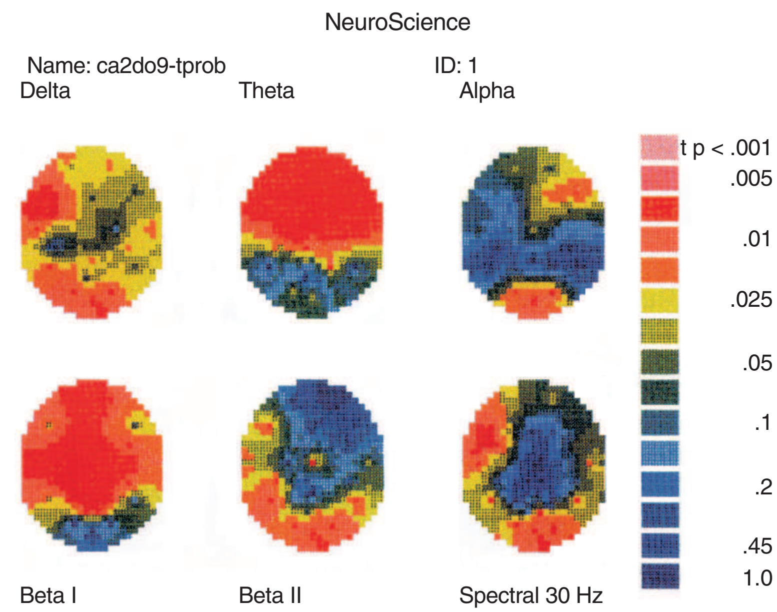


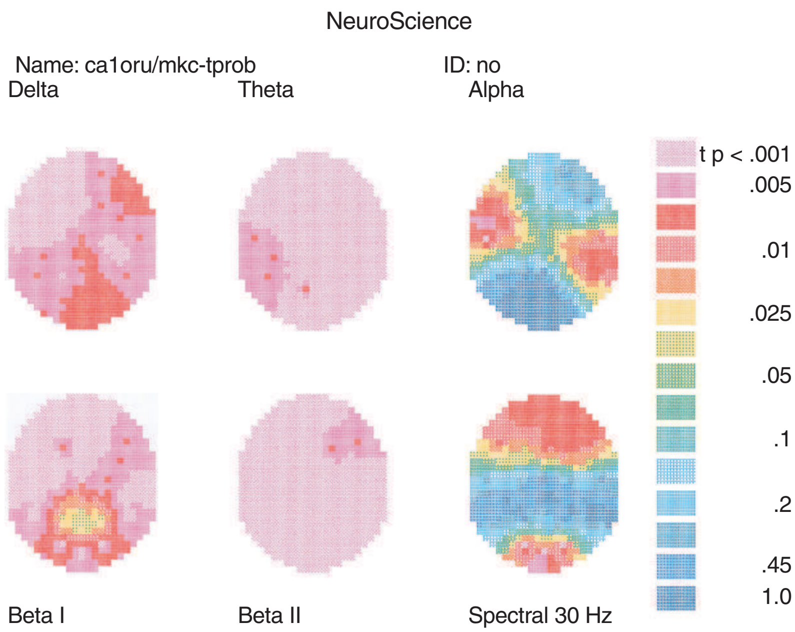
Figure 9 shows the pre/post cannabis music changes in the GA mappings for the four subjects. Post-THC-decrease of δ-, θ-, and β-amplitudes was a constant observation throughout the individual averages of the four subjects and was observed in GA of the four persons, as well. Comparing the left with the right mapping, higher amplitudes, especially on δ- and θ-range in the upper row, but also on central parietal β areas below, were observed in the left pre-THC mapping. In temporal areas, the θ-decrease is remarkable (Figure 10).

Pre-THC-music listening caused an increase of θ-percentage compared to the resting state. In the post-THC-music maps, the percentage decreased in central and frontal regions more than in rest condition, but most decreases appear in both temporal regions.

As seen before, significance mapping of individuals showed highly significant changes ($p < 0.001$) between pre-THC-rest, pre-THC-music and post-THC-music (Figure 11).

Comparing the GA of the 4 subjects a significance of $p < 0.025$ on α-range for the left occipital region was detected. Pre-THC-rest compared to post-THC-music showed a small change in the left occipital area, as well as the comparison of pre/post GA of music listening. This particular region around

FIGURE 6. Significance Mapping T-Probabilities EEG-Changes Rest to Music



O1 (left occipital electrode) showed a faster frequency in the spectral map. The occipital region is known to show changes under the influence of music (Konovalov and Otmakhova 1984; Petsche 1994; Walker 1977). In this context, the change of occipital alpha might indicate changes in visual association linked to music. This region should be investigated with further studies (Figure 12).

Comparing pre/post music listening over four subjects, a significant change ($p < 0.025$) at electrode T4 (right temporal lead) was observed. It seems that the θ-decrease over the temporal lobe reported above is more prominent in the right hemisphere. Comparing post-THC-rest and post-THC-music GA, a small change in this temporal area was also observed on β-1. This region seems to change constantly with all four subjects and should be regarded as a region of interest with combined methods such as PET and EEG. Several studies noted observed changes in the right temporal fronto-temporal lobe, but with varying frequency ranges (Auzou et al. 1995; Bruggenwerth et al. 1994; David et al. 1989; Duffy, Bartels, and Burchfiel 1981; Petsche 1994; Petsche, Pockberger, and Rappelsberger 1986; Petsche, Pockberger, and Rappelsberger 1987). Even results of dichotic listening indicate changes in the right hemisphere (David et al. 1969; Davidson and Hugdahl 1996; Kimura 1967). Alterations in the temporal lobe EEG might represent changes in the hippocampus region as

FIGURE 7. Amplitude Mapping Rest Alpha Changes

Rest: Pre/Post-THC-Alpha

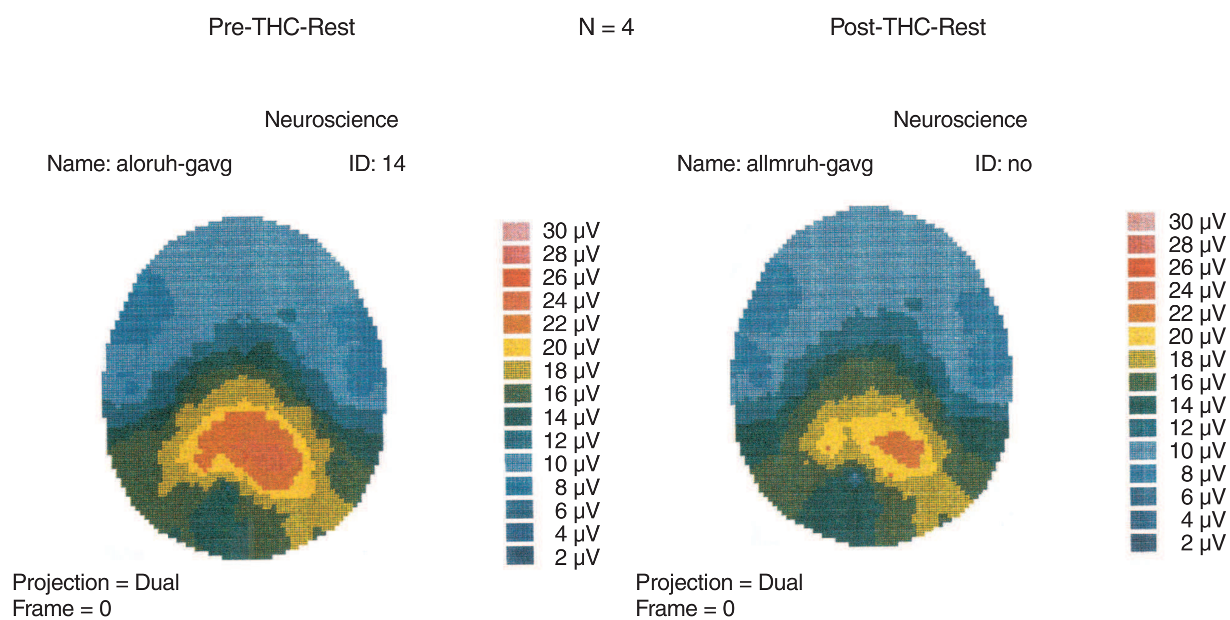


FIGURE 8. Amplitude Mapping Music Alpha Changes

Music: Pre/Post-THC-Alpha

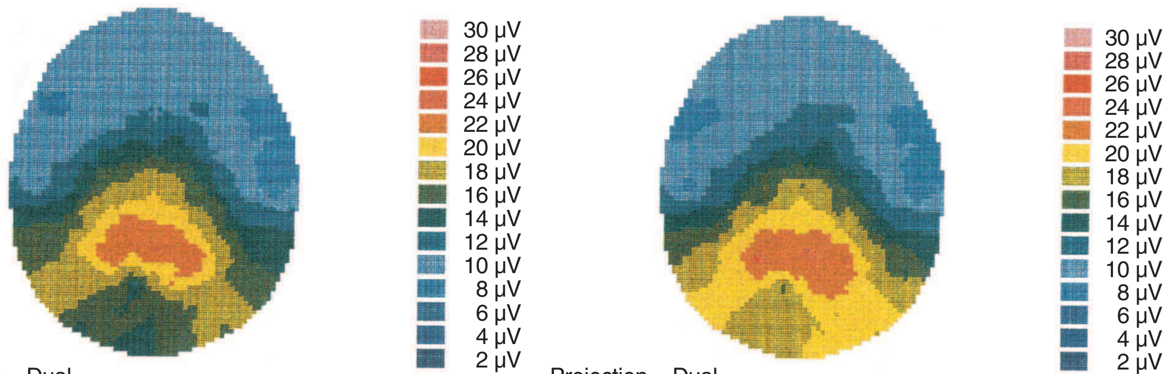
Pre-THC-Music N = 4 Post-THC-Music

Neuroscience

Name: alleohn-gavg ID: 14

Neuroscience

Name: allemjt-gavg ID: 14



Projection = Dual
Frame = 0

REAL TIME EEG Frequency: Alpha Dynamic Range: 256 µV

Projection = Dual
Frame = 0

REAL TIME EEG Frequency: Alpha Dynamic Range: 256 µV

FIGURE 9. Amplitude Mapping Pre/Post-THC Music Changes

Music: Pre/Post-THC-Changes

Pre-THC-Music Gavg N = 4 Post-THC-Music Gavg

NeuroScience

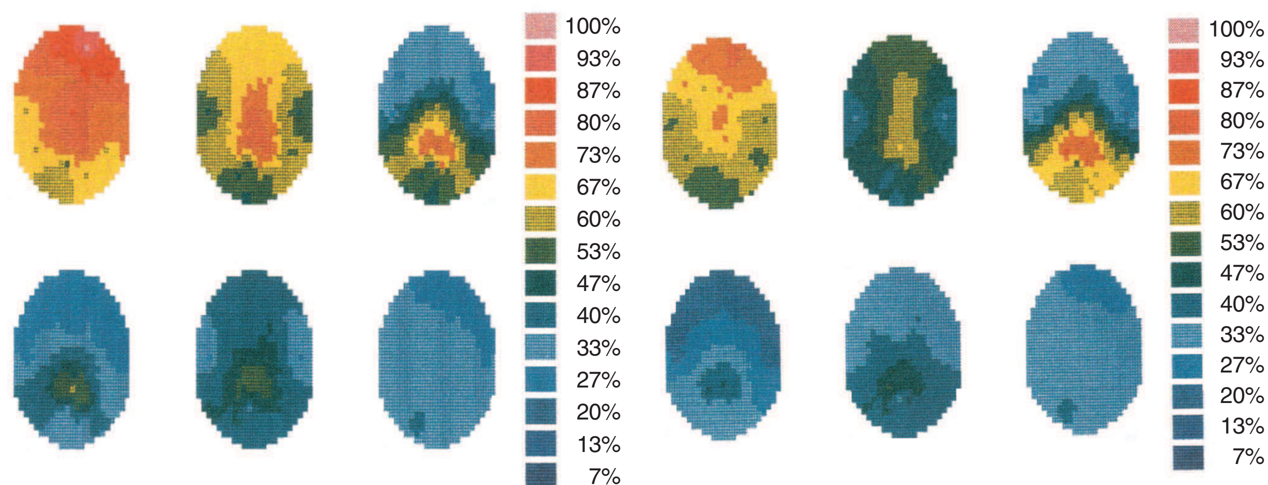
Name: alleohn-gavg ID: 14

Delta 30 µV Theta 15 µV Alpha 30 µV

NeuroScience

Name: allemit-gavg ID: 14

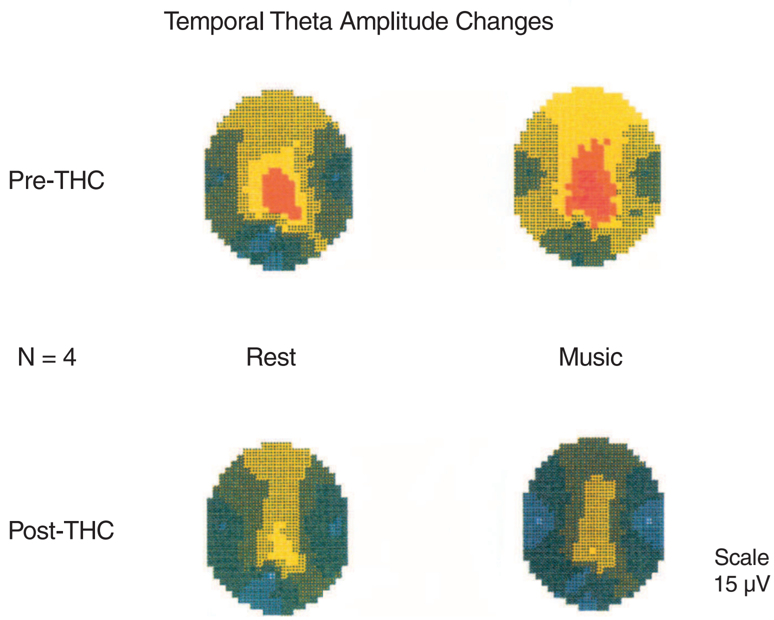
Delta 30 µV Theta 15 µV Alpha 30 µV



Beta I 15 µV Beta II 15 µV Spectral 30 Hz

Beta I 15 µV Beta II 15 µV Spectral 30 Hz

FIGURE 10. Amplitude Mapping Theta Pre/Post-Music and -Rest



well. It is rich in cannabinoid receptors and has a strong impact on memory functions and information selection.

DISCUSSION

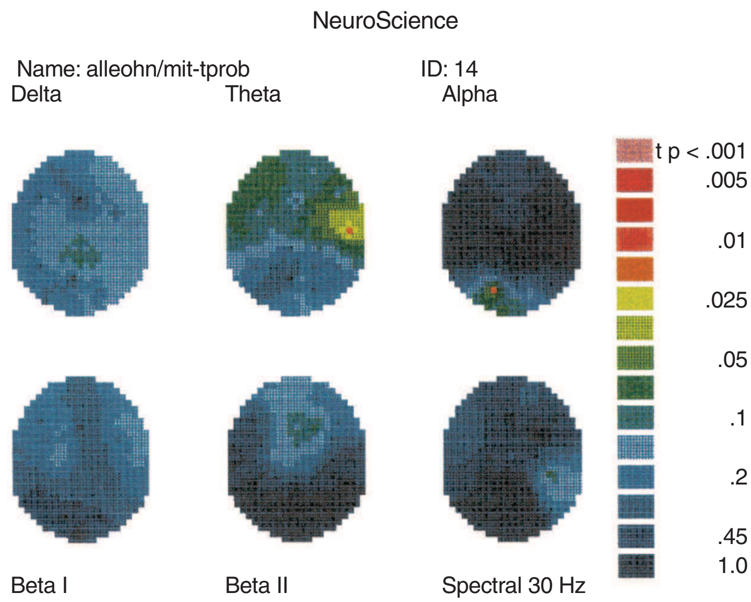
Changes in Temporal Areas

Comparing pre/post-THC-music, differences ($p < 0.025$) were found in the right fronto-temporal cortex on theta, and on alpha in the left occipital cortex. During pre-THC-music listening theta-percentage increased, but decreased more in post-THC-music than during rest. In both temporal lobes, theta-amplitudes decreased during post-THC-music as well. Significant ($p < 0.025$) changes in temporal and occipital areas and increasing alpha signal strength in parietal association cortex seem to represent a neural correlate of altered music perception and hyperfocusing on the musical time-space.

Holonomic Memory Function, Time and a Metric Frame of Reference

Webster has claimed a "different manner of retrieval" in memory function during states of cannabis consciousness that are not organized in a sequential

FIGURE 11. Significance Mapping, Temporal and Occipital Areas (p < 0.025), T-Test Pre/Post-THC-Music, (N = 4)



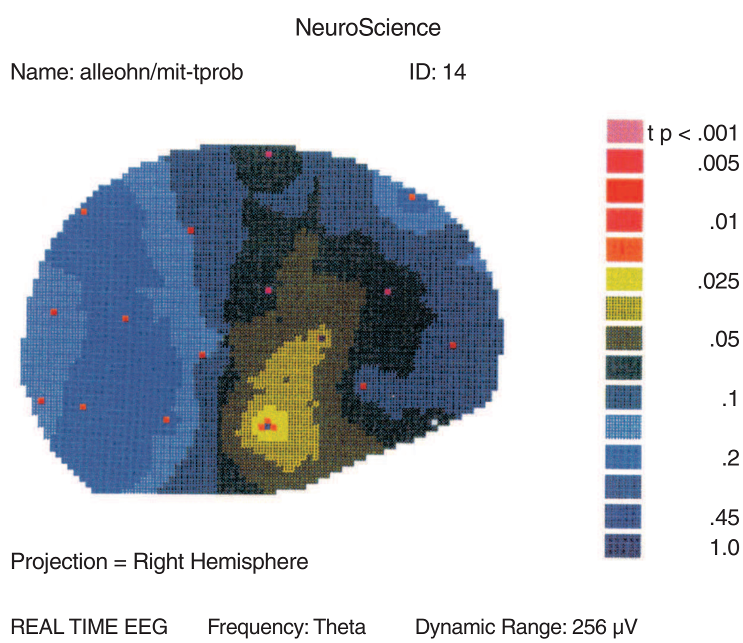
linguistic, but a more holonomic order (Webster 2001, p. 98) and in music, as an aesthetic and gestalt-oriented manner during music perception. Weakening of hippocampal censorship function and overload competing of neuronal conceptualizations during information selection (Emrich et al. 1991) might be connected to cannabis-induced prolonged time estimation and intensity scaling. This metric reference promotes functions of a divergent cognitive strategy to overlook the Gestalten of musical holonomic symbolization on one hand and to lose track (Webster 2001) on the other, because convergent perception of sequential information parts is reduced.

Mathew reported a cannabis-induced change of time sense CBF correlated with changes of cerebellum blood flow (Mathew et al. 1998). Cerebellum is associated with movement organization and time-keeping functions. Music as a *Zeitgestalt* (Zuckerkandl 1963) is an art that is connected to the act of performing (Aldridge 1996), to a playing of an instrument or, rather of a musically used sound source. Music can only be heard in time. One gestalt that might be perceived more intensely in "cannabis consciousness" (Webster 2001, p. 99) is one fundamental element of music, the rhythm. A good picture of these processes was given by one of Anslinger's co-workers (Sloman 1998, pp. 146-7):

> Yeah, but why would he [Anslinger] want to get after them?" Sloman wondered. "Because the chief effect, as far as they were concerned, is that it lengthens the sense of time, and therefore they could get more grace beats into their music than they could if they simply followed a written copy." Munch had completely lost Sloman right out of the gate. "In other words, if you're a musician, you're going to play the thing the way it's printed on a sheet. But if you're using marijuana, you're going to work in about twice as much music between the first note and the second note. That's what made jazz musicians. The idea that they could jazz things up, liven them up, you see.

Rhythm is connected to internal kairological and external chronological time processes (Aldridge 1989). Those expanded auditory metric units as proposed by Globus et al. (1978) promote a frame of reference that seems to fit more precisely into an audio-visual way of perceiving acoustic relations. The drummer Robin Horn said (Boyd 1992, p. 205), "it (pot) does create a larger vision, and if that's the case, then it would apply to your instrument because

FIGURE 12. Significance Mapping T-Test Pre/Post-THC-Music (Red dots represent electrode positions) N= 4, Right Hemisphere Theta Change ($p < 0.025$)



the more you see, the more you can do." Changed left occipital and right temporal EEG activity might represent such a change of auditory perspective on musical acoustics as reported above. It seems that this change of auditory perspective in perceiving musical *Gestalten* (Webster 2001) is mediated throughout an extension of auditory metric scaling during internal sound staging of music perceived. Listening to a record via headphones becomes a much more 3-dimensional moving soundscape, there seem to be "greater spatial relations between sound sources" as Tart identified a characteristic cannabis experience in the state of "being stoned" (Tart 1971, p. 75).

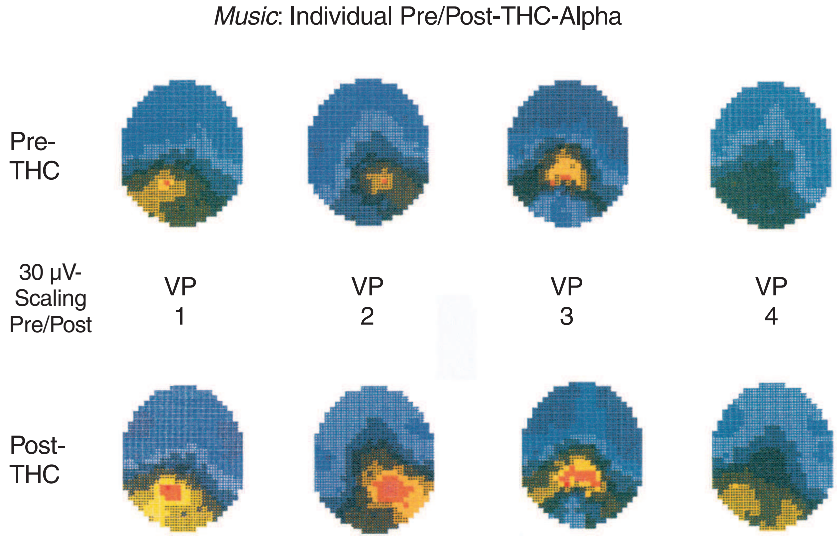
Hyperfocusing on Sound

A comparison of the individual pre/post averages subjects showed intra-individual stable EEG-Gestalt, for one subject even in the follow-up. Intra-individual stability of the whole EEG-Gestalt in rest and activation replicated findings on personality and situational sensitivity of the EEG (Davidson and Hugdahl 1996; Hagemann et al. 1999; Koukkou and Lehmann 1978; Machleidt, Gutjahr, and Mügge 1989). The α-focus in parietal regions showed individual topographic shapes of receptive activity. This indicates personality factors represented in the EEG, but changes on α-amplitude clearly suggest a functional intensification of individual hearing strategy (Figure 13).

Following Jausovec (1997a,b), we can observe more effective information processing. Alpha amplitude changes show a marked similarity to "reverse alpha" findings in studies with gifted individuals. Jausovec associated higher α-scores with a more efficient information processing strategy, less mental workload and flow. Curry (1968, p. 241) proposed a "hyperfocusing of attention on sound" as an explanation for changes in the figure-ground relationship while listening to music. This cognitive change of hearing strategy might be mediated via changed time perception for the rhythmical grid and synchronically expanded intensity scaling for frequency patterns in acoustic relationships. de Souza described a cannabis-induced change of preference for higher frequencies (de Souza et al. 1974). High frequencies represent overtone patterns and provide, along with time delay patterns, localization information about sound sources in acoustic space. This preferred focusing on higher frequencies might result in the way an enhancer or exciter in studio technology works.

No wonder some dub and psychedelic music is produced with virtually moving soundscapes with reverb and delay effects. It permits the creation and manipulation of "sound staging effects" (Moylen 1992) adequate to the state of a cannabis high. A distinct handling of sound effects is basic for good music recording and shows the skills of an experienced engineer. The development of audio-technical studio equipment and popular music in the 1960s went hand

FIGURE 13. Amplitude Mapping Pre/Post-THC-Music Alpha Gestalt (VP = Subject 1, 2, 3, 4)



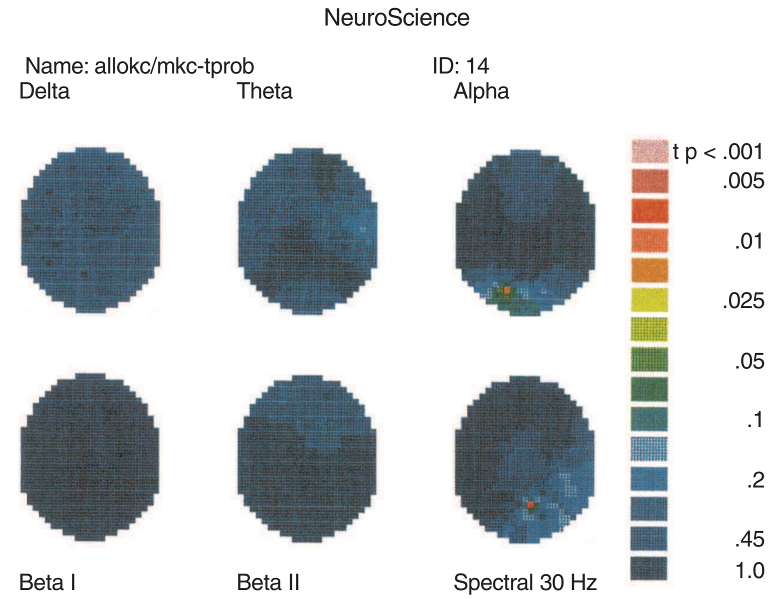
in hand. Ideas in soundscape creation stimulated discovery of new techniques in audio engineering. Intensive exploration, design and staging of sound sources in their spatial relation are essential for attainment of a certain sound of the recorded music (Martin and Pearson 1995).

"Are You Experienced?"–Learning and Cerebral Listening Strategdy

Looking at the process of listening, highly significant pre/post changes ($p < 0.001$) while listening to the first piece of music have been observed comparing individual averages in the T-Test, but significance decreased for the second and third piece in the experimental sequence (Figure 14). Changes in temporal areas on α-frequency indicated a change in auditory processing. A significant change ($p < 0.01$) comparing GAs of spectrum frequency at the right parietal-occipital electrode PO2 suggested a change in neural processing speed in this area. This right parietal-occipital change was observed for the first piece of music in the sequence and might indicate the onset of a changed cerebral listening strategy.

The experienced user of cannabis effects might be able to use the cannabis-induced altered auditory meter and intensity as an artist for aesthetic purposes. Becker in his analysis of jazz musician behavior and drugs explained how cannabis effects have to be perceived, learned, and domesticated before

FIGURE 14. Significance Mapping Pre/Post-THC for the First Piece of Music (King Crimson) N = 4



using them effectively (Becker 1963), and being able to switch those relation patterns off when needed (Weil 1998; Weil, Zinberg, and Nelsen 1968). A skilled and trained musician might benefit from "losing track" (Webster 2001) during an improvisation and even while playing composed structures. This method of reducing irrelevant information offers spontaneous rearrangement of a piece, vivid performance with enlarged emotional intensity scaling, and the opening of improvisational possibilities by breaking down pre-conceptions and restructuring habituated listening and acting patterns (Fachner 2000).

However, the cultural and aesthetic use of these inspirational possibilities is illegal, and was one reason for prohibition and incarceration of many jazz musicians, painters and actors (Musto 1997; Sloman 1998). The potential use of cannabis-induced perceptual functions for medical purposes seems to be obvious. Hearing loss could be affected by stimulating the cannabinoid receptor function for retraining purposes, as suggested from tinnitus research. Tinnitus patients suffer from continuously present frequency patterns, which could be mentally reduced by systematically ignoring them (Jastreboff, Gray, and Gold 1996). Conversely, it might be useful to investigate described cannabis-induced psycho-acoustic enhancing effects for re-training high frequency ranges in hearing loss.

CBR Activity, "Reverse Alpha" and the Cannabis High

Compared to pre-THC-rest and pre-THC-music in the post-THC-music EEG a rise of alpha percentage and power was observed in the parietal cortex on four subjects, while other frequencies decreased in power. Alpha amplitude changes are similar to "reverse alpha" findings in studies with gifted individuals (Jausovec 1997a,b; Jausovec 1998). In these studies, the degree of mental workload and effectiveness of problem solving seemed to be represented by the α-amplitude. An increase marked less mental workload in appropriate brain areas whereas a decrease would represent increased workload. Present results give reason to conclude that music seems to be processed more easily with cannabis than without. The rise of average α-amplitudes about 4 μV might be a neurophysiological indicator for the so-called state of "being high" (Solomon 1966). That auditory information seems to be processed more easily would be another argument for using cannabis as a supportive hearing aid. Alpha-results and changes in audiological tests reported above, user reports (Grinspoon and Bakalar 1994; Mezzrow 1946; Shapiro 1988; Webster 2001) and suggestions (Boyd 1992; Tart 1971) offer evidence of possible benefits that should be researched.

A possible mechanism of this increase of α and decrease of other frequencies might be explained through CB receptor findings. Animal research has shown a cannabis-induced decrease of somatosensory evoked potential (SEP) amplitudes (Campbell et al. 1986). A decrease of amplitudes has been observed in other EEG studies as reported above. The EEG represents postsynaptic dendritic potential summation of cortical cells (Niedermeyer and Lopes de Silva 1993). Postsynaptic cannabinoid receptors are known to imitate GABA-inhibition to reduce cell-firing rates (Joy, Watson, and Benson 1999). Decreased amplitudes in this EEG study might represent a decreased cell-firing mode caused by cannabinoid receptor mechanisms. Further research is needed to prove this speculation of the cannabis-induced decrease of EEG amplitudes. We have observed decreased amplitudes on δ-, θ- and β-frequencies over most parts of the brain, but α-amplitudes also decreased in frontal areas.

Struve has proposed an alpha hyperfrontality as a residual effect of heavy cannabis consumers (Struve, Straumanis, and Patrick 1994). In comparison to a normed-database alpha-rest activity seemed to exhibit more frontal alpha-power in heavy consumers. Rest-EEG here was not compared to a normative database, but more alpha power could not be observed in this study during musical perception or at rest.

Only in parietal parts of the brain did we observe an increase of α-power. This might be due to the intentional listening process, which might be enhanced by cannabis effects, but this reverse relationship of increased ampli-

tudes in parietal areas during stoned music listening and decreases in most other areas of the brain seems to be a typical action mechanism that represents this cannabis-specific state of perception and aesthetic cognition. It reduces energy and permits a more effective processing of the intentionally perceived content. This might be reflected by increased parietal α-power and represent cannabis-induced increased cell firing mediated by CB receptor activity.

Time perception seems to work in this reverse manner, as well. The inner clock seems to speed up while time sense seems to expand. For musicians, this might work like a real-time time-lens, allowing more space between the notes during improvisation or sound design during mixing.

Cannabis as a Hearing Aid?

If one can perceive music, much "better" than before, why should not the hearing impaired also improve? Results reported in the literature and shown in this EEG experiment suggest that cannabis could be used as a hearing aid. It seems that acoustic properties of sound may be enhanced by cannabis. It permits a more effective spatial distinction between sound sources, which is of importance in hearing loss. Significant changes in temporal and occipital areas support this assumption. These changes represent an altered auditory perspective on musical acoustics, and should be taken into account for further research on cannabis-induced enhanced acoustic perception.

Furthermore, the increased α-percentages over the parietal cortex, which might indicate an intensified perceptual strategy with less mental workload, could be used for training programs with hearing-impaired persons. Acquired hearing loss in high frequency ranges could be compensated throughout reactivating and relearning acoustic memory shapes. In certain training courses cannabis could be used to intensify the cerebral hearing strategy of the hearing impaired person. This cannabis effect might help hearing-impaired persons to compensate lost abilities and enhance brain plasticity. However, by discussing possible benefits of cannabis-induced alpha enhancing during attention processes, we have to bear in mind that there are individuals, which show much less or even no alpha in their EEG (Niedermeyer and Lopes de Silva 1993).

Thaler's study showed highly significant improvement for a hearing impaired person on an audiological Word-Test. Others report that prosodic differentiation seems to be enhanced. In view of the fact that spoken language is based on nonverbal musical elements, and that supra-segmental and prosodic features constitute the sound of the human voice (Aldridge 1996), it is possible that it is easier for a hearing-impaired person to catch the meaning of a sentence after having smoked cannabis. Speech perception enhancement might be of interest for aphasia research. Further research is needed to explore possible benefits of cannabis for the hearing impaired.

CONCLUSION

This study gives promising insights into quantified EEG changes of pre/post-THC music listening as provided by amplitude and significance Mapping over averaged EEG epochs of music. Results are not based on a high number of subjects but on ethnographic EEG correlation of "stoned" listening to music. Accompanying this process in the life world provides naturalistic authenticity of tendencies occurring during those processes. Further laboratory research could compare several issues reported and discussed in this ethnographic intervention.

Changes in temporal and occipital areas and increasing α-signal strength in parietal association cortex seem to represent an inter-individual constant EEG correlate of altered music perception and hyperfocusing on the musical time-space.

Post-THC increase in parietal α-percentage showed a marked similarity to reverse α-findings in studies with gifted individuals and might represent a more effective strategy in task-specific information processing.

Cerebral change of perception seemed to be initially indicated throughout the significant spectrum change on the right parietal-occipital electrode, as well as all over changes of temporal and occipital areas, both involved in auditory perceptual changes.

Changes in occipital areas might indicate an enhanced acoustic "insight into the space between the notes" mediated throughout desynchronization in the visual association cortex. Together with the right parietal cortex, this area should be further examined in investigations with combined PET scan and EEG. Theta changes in temporal areas might indicate altered metric intensity scaling during hippocampal censorship of sensory data sets.

Basic research on cannabis-induced auditory changes seems to be indicated to estimate possible benefits for the hearing impaired. Enhanced perception of musical acoustics as perceived in prosodic and suprasegmental properties of speech might be of interest for aphasia research.

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An Interview with Willem Scholten and Myra Klee: June 26, 2001

Ethan Russo

Russo: Firstly, for our readers, would you be able to tell us what the reason was for beginning this particular program.

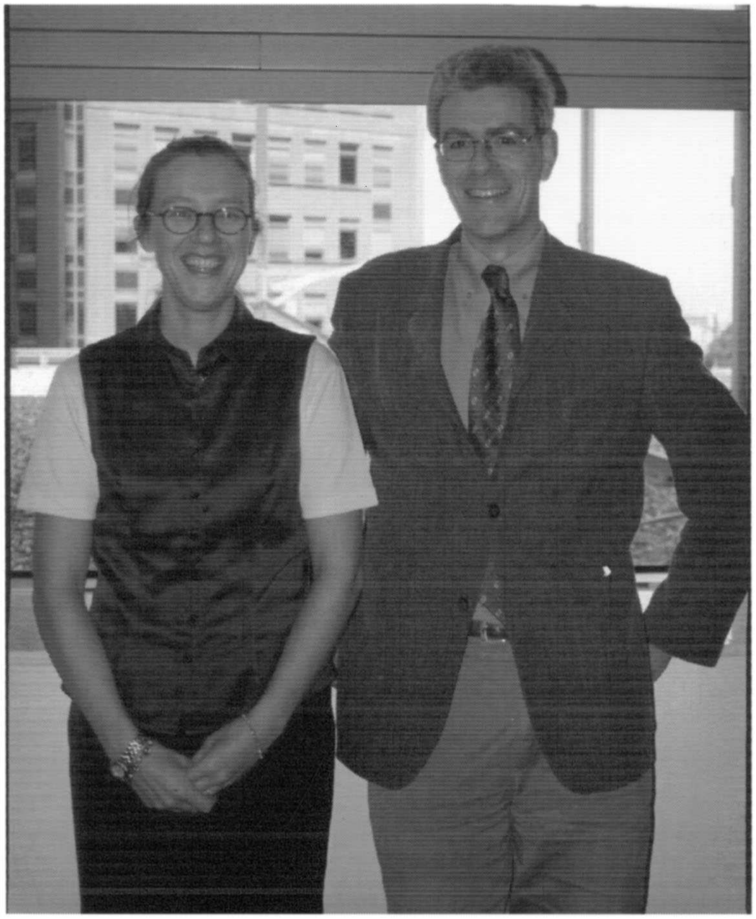
Scholten: Well, actually, in other countries as in the Netherlands, many patients experienced that cannabis had beneficial effects on their disease. As it is now, prescribing and delivering cannabis as a medicine is prohibited. So, patients asked politicians, "Please, can we use cannabis as medicine?" We had some discussion on that, and our ministry then asked for the Health Council for an overview of the evidence for using cannabis as a medicine. The Health Council made an overview [of the literature] from 1970 to 1995, and concluded that there were many studies, but that almost all of them were case reports. Many did not state what was used in this particular case, so sometimes there wasn't even any mention whether it was cannabis or THC, and when they used cannabis, they didn't specify the THC content of it, or what was CBD. So, the advice of the Health Council and its advisory board to the government was that there should be more trials, and if done, it should be with clearly defined cannabis, or the purified substances out of the cannabis. Then our minister adopted that advice, and decided that there also should be a legal source for the cannabis. The Single Convention [of the United Nations] says then that there should be a government agency that acts as a regulator. So, it was the conclusion that we should form the Office of Medicinal Cannabis.

Russo: Very good.

Ethan Russo is affiliated with Montana Neurobehavioral Specialists, 900 North Orange Street, Missoula, MT 59802 (E-mail: erusso@blackfoot.net).

Willem Scholten and Myra Klee are affiliated with the Department of Pharmaceutical Affairs, Office for Medicinal Cannabis, Parnassusplein 5, P.O. Box 20350 EJ, The Hague, Netherlands (E-mail: Wk.scholten@wxs.nl, m.klee@minvws.nl).

Myra Klee, Willem Scholten, The Hague, June 6, 2001



Scholten: Let me add the government decided to establish such an agency at the end of 1998. We made some preparatory work and it was formally established in March 2000. We started functioning as a government agency in sense of Article 28 of the Single Convention on the first of January of 2001.

Russo: I've heard previously that doctors in the Netherlands had less interest in pursuing use of cannabis with their patients. If that is the case, could you tell me why it is that they have been less interested than doctors in other European countries or in North America?

Scholten: Well, I'm not sure whether that is the case. I think in general, it is not confined to the Netherlands as a general tendency for doctors to be interested more in purified substances, chemical medicines, than in herbal medicines. Well, I always think that it's like the difference between opium and morphine tablets, which are accepted almost all over the world. In every country, morphine is accepted internationally, and cannabis is not.

Russo: So, in the Health Council's examination of the previous evidence, they did not look at information before 1970?

Scholten: Right.

Russo: So there was no examination of the extensive 19th century evidence in the literature. That was not taken into account?

Scholten: That's correct, but the older literature is not really the evidence we need for accepted medicines today. Of course, we know that cannabis was already mentioned in Chinese literature from 5000 years ago. But today, we require double blind cross-over placebo-controlled research in clinical trials. Prior to 1970, that wasn't done. Before I worked on cannabis, I worked on classical things and I've seen a lot of literature from before 1970 and even in the 70's that the methodology of performing clinical trials was very bad compared to today's standards. Well, often they were placebo controlled but without enough power to prove the efficacy, and so on. But, there is another aspect, and that's that the trials never had been done with standardized products, and that's true even for newer trials. That's still the problem.

Russo: Would it be fair to mention that those preparations were not available to any clinician?

Scholten: I think so. That brings me to the point that I can explain to you how our plan is to work, because this is exactly the problem. If you want to do a clinical trial you have to do that with a clearly defined preparation. The main thing is that it's clearly defined and that it's reproducible. So you have to prepare an assay of the main cannabinoids in the preparation and to make fingerprint of the rest. If you only required that, you could take seized cannabis from the police, but then you have a problem if you say in the end, "Well it worked fine," so that we can give it also to other patients. You have to conclude that the next cannabis that is seized by the police may have different properties. So, you have to start by growing the cannabis, and to use well defined breeds, to grow in well-defined circumstances. Then you have plans that you can reproduce every time. Then you make preparation according to pharmaceutical standards for use in GMP [Good Manufacturing Practice], and you test it with GCP [Good Clinical Practice], and so on. Then you can come to conclusions

that you have a preparation that works, and if you can register it, complying with the normal standards that are required for every drug.

Russo: In the Netherlands, are other herbal agents accepted as medicine?

Scholten: Some are. The problem is that, in many cases, the efficacy is not shown very well. And for other herbal preparations, the problem is that manufacturers say, "Well we cannot make enough profit for it." But, we think it's possible by using patented extraction methods by using registered plant breeds to protect the product that the manufacturer will profit commercially in the end.

Russo: So would that be the situation with, for example, *Ginkgo biloba* or St. John's wort?

Scholten: I think gingko is a very nice example. In the Netherlands we have an extract that is patented and that is registered at the same level as many chemical drugs.

Russo: What would you anticipate or is there an identified source now for cannabis that meets the criteria that you discussed?

Scholten: Oh, we hope so. I think Myra can explain a little bit.

Klee: We have had communication with several growers, and we will try to find a grower that is capable of growing standardized cannabis, and somebody who we can trust, then we'd like to offer a contract. Hopefully there could be two or three companies. Everybody has got their institute that can investigate seeds, so hopefully we will have one or two growers.

Russo: Would these be here in the Netherlands?

Klee: Yes.

Russo: I had read something on the Internet, and I would be the first to admit that it's not always a reliable source, but it implies that the first material had actually been sent from the U.K.?

Scholten: No. The articles in the newspapers about this were wrong. We had our first importation of cannabis plants, but they were imported for scientific purposes, and not meant for medical application.

Russo: It is fair to ask the source of that material?

Scholten: Well, it's a government agency. We act also for other parties, so I don't want to make any statement about the character of the plants. I hope that you can understand.

Russo: Surely. Once a source is identified, what would be the procedure for patients and their physicians to utilize the material? Would it only be used in clinical trials, initially?

Scholten: Yes initially, and after that I hope we can interest a pharmaceutical company in the development of a new medicinal product and have it registered, comparable to licensing in the United States. And, as soon as it is registered, it can be marketed through pharmacies. Then it can be a prescription drug like, for instance, morphine tablets.

Russo: If someone had material that was assayed and reproducible, and they had a clinical trial for a certain diagnosis, and it was successful, how long would you anticipate would be needed to allow actual prescription of the medicine?

Scholten: Well, we hope it will be done in several years, I think in 4 or 5 years. Although the product still has to be developed, it's not the same as with new chemical entities. Then we would have to do all the safety assessments. I think with cannabis-based medicine, it is already clear that cannabis is not a very dangerous substance. Of the fresh herb, you can eat your own weight, and only then would there be a risk of dying of intoxication. In the longer run, cannabis is not among the most dangerous substances. What has to be done by a manufacturer is to ensure that his preparation has comparable properties, and it's easier than starting from the beginning in showing that the substance is safe.

Russo: Is it your belief that different strains of cannabis are more effective than others for a certain condition?

Scholten: Yes, I think so. That's why we require that cannabis use is standardized. If all the strains acted the same, you wouldn't need to standardize.

Russo: Yes. Are there steps underway to actually encourage clinical research?

Scholten: Yes. (Aside to Ms. Klee in Dutch.)

Klee: We have meetings with pharmaceutical companies, as well as with growers. We try to encourage the pharmaceutical companies to develop medicine. This can cost a lot of money, so their first question is how you can profit from it. We hope we will have one or two pharmaceutical companies interested soon. There are some smaller trials at the Free University Hospital of Amsterdam. One was just recently finished. Then, hopefully in September [2001] will come follow-up. We provided a small subsidy for it, to then compare smoking with tablets.

Russo: What is the disease that they are studying?

Klee: Multiple sclerosis.

Scholten: There are four main targets. We will start with the most promising indications. We said multiple sclerosis is one of our targets, cachexia in AIDS and cancer, and nausea and vomiting in radiotherapy, and later we added chronic pain.

Russo: Would it be fair to say that everything in the program is set up to comply with the Single Convention as it currently is written?

Scholten: Yes, I think we have to comply with two things. One is the Single Convention and the other, higher pharmaceutical standards. I think both are very important because you will not succeed if you don't comply with those standards. You also need to convince other countries that this is important, and if you don't comply with international standards they will say what you did is amateuristic.

Russo: Why is it important that the Netherlands be able to show other countries that there is efficacy? Is this a philosophical belief, or just trying to share your expertise with other countries that are not as advanced in the process?

Scholten: Well, it's not necessary that we show other countries that it's efficacious. The Netherlands is a small country with a little more than 16 million people. So the Dutch market is large enough to develop a profitable medicine, except if you market at a huge price. [Laughs]. We hope that it will be affordable to everybody. Then you need to cooperate with other countries that share the same insights.

Russo: Do you feel that current international law has interfered with research on cannabis?

Scholten: Well, I think modern insights are not the same as when the Single Convention came into force. You see, the scheduling of cannabis in the Single Convention says that there isn't any medical application for it, that it is Schedule 1. Schedule 4 also says it's among the most dangerous drugs. I don't think that the international community would say the same thing if it had to be rescheduled today. On the other hand, we also need to have scientific evidence, so it makes it important that what we are doing is done in a methodologically good, acceptable way.

Russo: It seems that as compared to the USA, where HIV is one of the indications of greatest interest in clinical use of cannabis, there seems to be less inter-

est in Europe, perhaps because it isn't so prevalent. Are you aware of AIDS patients in this country using clinical cannabis?

Scholten: Oh yes, there are. We have an advisory committee to our office . . .

Klee: They will meet today. They come together every two months. We have subjects that are interested on the agenda, and there are representatives from the ministry, and also from several patients groups. They also have somebody from the multiple sclerosis group and one of the HIV patient groups.

Russo: Looking at another subject, it's my feeling that Americans receive some very biased information and half-truths about drug policy in the Netherlands. Is there any effort that your government is putting forward to try and make things clearer so that there are not these misconceptions?

Scholten: Let me first say that our office is part of the pharmaceutical affairs department and we have a separate addiction care department. I don't have clear detailed knowledge of the addiction care part of cannabis, but we make a lot of fact sheets and so on, and they are also available on the Internet.

Russo: Would you care to comment on General McCaffrey's visit to this country? Was there much fallout after that in terms of policy?

Scholten: Well, I don't think I should need to comment on McCaffrey's journey. Compared to other countries, our [drug usage] results are no worse than those in other countries. For instance, in the *British Journal of Psychiatry* [(MacCoun and Reuter 2001)], there was an article that compared different countries and the Netherlands was doing no worse than other countries.

Russo: Very good. Do you feel that cannabis tourism has been a problem and, if so, in what way?

Scholten: Well, it is not really an issue of medicinal cannabis, of course. I think it affects the use of medicinal cannabis in a sense that we want to separate medicinal cannabis and recreational use of cannabis. That's because we don't want to stigmatize patients as drug users. So, that's also why we placed our office in the Pharmaceutical Affairs Department and not the Addiction Care Department.

Russo: In that regard, do patients now currently go to coffee shops to get their cannabis?

Scholten: Yes, at the moment there is no special status for medicinal use of cannabis. So, you just buy cannabis and it's not marketed for recreational use

or for medical use. Everybody who wants to buy cannabis can go to coffee shops and use it in a medical way or in a recreational way. It is illegal.

Russo: But, they are limited, as anyone else would be, to 5 grams per purchase?

Scholten: Yes. Although the use of cannabis in the Netherlands and trade in it is prohibited, our prosecutors have a priority policy that they only want to prosecute bigger cases. Officially we have declared that under 5 grams, nobody will be prosecuted.

Russo: Following from that, what are the laws or the understandings about patients' ability to grow their own plants?

Klee: The same as for other people.

Russo: And those are?

Klee: Those are five plants maximum a person.

Russo: There is no limitation on how large they are or whether they are indoors or outdoors?

Scholten: No, people can be very creative by making their plants large. In practice, I don't think people will make very large plants. I think from a medical view there is another problem. It's not a legal problem. If you say people need standardized cannabis to treat their disease to know what they can expect, of course, they can have to some extent beneficial effect from their home grown plants too, but they will not be able to standardize to a very high degree. In the end, that can be a problem. For instance, if you're a patient with multiple sclerosis, and you use cannabis as medicine, you don't want to become high. You want the symptoms to be treated without becoming high, so then you can do your work. What I hope is that we are able to find breeds to make extracts from the cannabis plant that treat the patients without making them high. If they grow their own plants now they will grow breeds that make them high. So then, it is not the optimal therapy.

Russo: I would like to have your comment on how the illegality of cannabis has prevented its exploitation or use as a medicine that might be valuable to certain patients.

Scholten: I think it's difficult to do clinical trials if you need to be licensed first to have the substance available. In the past it was very difficult to get such a license, so this interfered with getting the evidence, but then it's just a circle.

Because there's no evidence, it is difficult to get the license. I think internationally we are in an era in which, in many countries, the governments are thinking about accepting just an objective clinical trial and assessment of the potency of cannabis as medicine. And if we have this, maybe the outcome can be negative or it can be positive, but then we have scientifically seen the value of it, and can then decide on that basis what to do in the future.

Russo: How has the policy of tolerance for cannabis helped lower crime rates?

Scholten: The Dutch policy recognizes a difference between hard drugs and soft drugs. Cannabis is a soft drug, one of the few. The others are hypnotics that are classified as soft drugs, and all the other drugs are hard. We have a policy of only tolerating soft drugs in coffee shops, but as soon as they sell hard drugs or alcohol, or sell to minors, the coffee shop will be closed, and also if they sell in too large amounts. So, we make a good separation in the cannabis markets and the hard drugs. This permits us to clearly see what's going on in the coffee shops. I think that has diminished crime and criminality in coffee shops, but of course it's always like a balloon. If you press here, it becomes wider another place. Every country has that problem; the criminality is in the hard drugs.

Klee: Although there is tolerance, Amsterdam is becoming more strict, in that they have reduced the number of coffee shops, especially within a certain area around schools. They said that for every coffee shop that's closing, nobody else is going to get a license for it. So, in the last year the number of coffee shops has been very much reduced.

Russo: This is a politically sensitive question, but has your office been criticized officially or unofficially by American agencies?

Scholten: Not as far as we know. To start, as an international agency we sent a letter to the United Nations to the INCB [International Narcotics Control Board] and we also sent it to many other countries via our embassies. We did not get any reaction from, for instance, the United States that it was not done in the proper way. On the contrary, formally we already had some contact with NIDA [National Institute on Drug Abuse] and they were somewhat positive about our plans, and I think they will accept what we are doing. I think it will do, at least as long as we comply with the requirements of the Single Convention.

Russo: Are there similar plans that you're aware of to do what you are doing in other countries in the European Union?

Klee: We see a lot of movements in other countries in Europe. In Spain, there are some regional parliaments that are trying to allow cannabis for patients. In Italy, something is going on, and in Germany is already there's a company who wants to do a trial. We are organizing an end of year conference and we would like to invite our colleagues from the different countries. We would like to express our view that it's important to do clinical trials that are randomized, double-blind. We hope that the other countries will also follow the way of the clinical trial with registration.

Scholten: The conference is meant for representatives of the other states, I think at maximum, at most thirty representatives.

Russo: In your program, for example, let's say that in the U.K. there is a clinical trial that is undertaken with a preparation that meets your specification, would you accept that result or must it be done in this country?

Scholten: The legislation on medicines is harmonized all over Europe, and as soon as one company has registration for a preparation at the Medicine Control Agency in London, it can be registered, in principal, all over the European Union within 3 months. This is called the Mutual Recognition Procedure. It is also possible that they apply at the European Medicine Evaluation Agency and then its registered all over Europe at one time.

Klee: It could be possible that this company is trying to register a medicine for multiple sclerosis, and may be at the same time a Dutch company is doing a trial with medicine for cachexia, for example.

Russo: Are you aware of any countries or programs in other countries, have they approached you about using their information? In other words, is there any movement that you're aware of by companies from other countries to introduce their medicines here?

Scholten: Marinol® is already on the special application basis. It's not licensed in Europe, at least not in the Netherlands, but if patients apply for it, it can be imported. I don't know of any other preparation that is marketed in Europe at the time.

Russo: Let's use as an example GW Pharmaceuticals. I understand that they have an Initial Public Offering now and they have trials underway in the U.K. If they have positive results, would you anticipate that they would approach you to use their preparation?

Scholten: Oh yes. It's no problem. If they register, it can be marketed in the Netherlands, too. Our philosophy is that drug development is always an inter-

national affair, an international concern. So it makes sense that if a Dutch company develops a product, it also has to do clinical trials in other countries, and GW needs to do clinical trials and needs our hospitals to find enough patients.

Russo: I believe in this article of yours [(Scholten 2000)], you mentioned that you might consider supplying cannabis for research in other countries, under existing law in the Single Convention. Is this really something you would anticipate doing? Under what conditions would you consider exporting cannabis or whatever kind of preparation that met these standards to a company or other countries for research?

Scholten: Well, the first condition is that the authorities of the other country give their consent. That's to comply with the international law. Furthermore, we need to be able to find growers for the amount they need. If they want a very large amount, we won't probably be able to produce it, but I don't think it will be a real barrier for cooperating with companies from other countries.

Russo: So, as it is written now, if a grower in the Netherlands wanted to take part in the program, and they had a standardized strain, agreed to sell all of the material to your agency and kept track of everything else, they would be able to do business and potentially supply to another country?

Scholten: In principle, they will able to do that. There is another condition and that's that we don't want any criminal involvement. So, every grower will be screened before we contract with them.

Russo: Is there any movement currently for Holland to withdraw from the Single Convention?

Scholten: No.

Russo: So that has not been discussed at all?

Scholten: No, no. Well, of course people sometimes suggest to the government to withdraw, but it's no real option, I think.

Russo: Is it true that medical patients get a discount in the coffee shops for their purchase of cannabis?

Klee: I read that somewhere that there are certain coffee shops that have this agreement.

Russo: Do you know what kind of documentation the patient needs to provide for that?

Scholten: I think it will be in writing from a physician to a coffee shop. It's not official, of course, because all of what those people are doing is illegal.

Russo: Is there any advice that you might be willing to provide to researchers in other countries as to how to initiate a program such as yours?

Scholten: Well, what I see as the main problem in the discussion on the use of medicinal cannabis is that they don't realize that research must be reproducible. So people often start at the wrong end, in my view. If you don't make a preparation that you can use again after doing a trial, you can only make a general statement as a conclusion, but you can't say that we will give the patient again the same material.

Russo: Can people get by that through the use of a cloned strain of cannabis?

Scholten: Well, if they specify enough, that could be a possibility, but the growing circumstances also influence the product and the extraction process. For instance, I heard of people making tea of cannabis using a little butter to enhance the solubility of the cannabis and cannabinoids. But, if patients do not know how much butter they add they make a different strength of the tea each time.

Russo: Are you encouraging any research on the use of vaporizers as an alternative to smoking cannabis?

Klee: Yes, of course. Smoking is not our first priority because it doesn't seem to be healthy, so, either a vaporizer or another medicine form. The trial that was done last spring showed that swallowing may not be the best solution, but a vaporizer could be. So it depends on the pharmaceutical company if they are able to develop the right dosage form. But, we realize that smoking is not the right way of taking medicine.

I also want to add something about your question from screening because we are, of course, not capable of screening growers for the things that they do in the future, but we are making a contract with them, and we are going to control this contract. Of course, we are able to stop the deal if something goes wrong, but we have tried to practice that way so we are screening before we give them a contract.

Russo: What is the level of interest among the growers out there in participating in your program?

Klee: I think the growers that we spoke with are mostly involved because they, or somebody in the family have a disease, and they became familiar with the

product. There is also an institute in a university. They have knowledge about it because they developed hemp breeds for rope.

Russo: Well I think that we went through the questions. Are there other comments that you would like to record?

Scholten: Well, I think we explained the way we are working and what the most important aspects are.

Russo: Thank you very much.

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The Medical Use of Cannabis Among the Greeks and Romans

James L. Butrica

ABSTRACT. This article, which contains a complete survey of the surviving references to medical cannabis in Greek and Latin literature, updates the last serious treatment of the subject (Brunner 1973).

Though it eventually became commonplace, cannabis seems to have been largely unknown to the Greeks in the fifth century BCE, when Herodotus wrote his description of the hemp vapor-baths used by the ancient Scythians, which constitutes the earliest reference in Greek literature. While its use in medicine is not attested until the first century CE, it was evidently well established by then. The Roman writer Pliny the Elder records several medical uses, but comparison with Greek writers suggests that he is sometimes mistaken, and there is no secure evidence for the medical use of cannabis by the Romans. Greek writers, on the other hand, report the use of cannabis in treating horses–especially for dressing sores and wounds–and in treating humans. Here we find the dried leaves used against nosebleed and the seeds used against tapeworms, but the most frequently mentioned treatment involves steeping the green seeds in a liquid such as water or a variety of wine, then pressing out the liquid, which when warmed was instilled into the ear as a remedy for pains and inflammations associated with blockages. Many sources also observe that the seeds, when eaten in quantity, dry up the semen; a passage in Aëtius shows that they could be prescribed as part of the treatment for teenaged boys (and girls) afflicted by nocturnal emissions.

A recreational consumption of cannabis seeds is attested first in the comic poet Ephippus in the 4th century BCE and again in Galen in the second century CE.

Ancient medical writers classified cannabis among foods with a

James L. Butrica is Professor in the Department of Classics at The Memorial University of Newfoundland in St. John’s, Newfoundland, Canada A1C 5S7 (E-mail: jbutrica@morgan.ucs.mun.ca).

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warming effect, foods with a drying effect, foods that harm the head, foods that thin the humors, and foods that prevent flatulence. It was acknowledged to have an intoxicating effect not characteristic of the seed of the agnus-castus, which was sometimes prescribed in its place.

Perhaps that intoxicating effect, and the prescribing of cannabis seed to teenaged boys, lies behind the controversy over the "proper" medical use of cannabis at which Galen hints when he says that its only proper use is to thin the humors through the urine.

KEYWORDS. Cannabis, medicine, Greece and Rome

This paper is intended to update our knowledge of the medical use of cannabis in the Classical world, a topic on which the only serious discussion is Brunner 1973 (largely repeated in Brunner 1977). While no previously unknown texts have been discovered in the meantime, the availability of the *Thesaurus Linguae Graecae* (a searchable database of ancient Greek literature developed by Dr. Brunner and others) now permits a more thorough investigation of the ancient sources than ever before; the result has been not only to reveal some additional treatments not known to Brunner but also to suggest a new understanding of some of the data.

Cannabis went by a variety of names. In the first century CE, Dioscorides 1907-1914, *Materia medica* 3.148 mentions *kannabion* (a diminutive form, "little cannabis," "dear cannabis"), *skhoenostrophion* ("rope-twister"), and *asterion* ("little star"). An ancient scholarly note on line 181 of Aristophanes' comedy *The Acharnians* says that *sphendamnos* was another name for cannabis because its fibres were used to make slings (*sphendonai*). Finally, the lexicon of Hesychius, compiled probably in the fifth century CE, adds *phalis* as another equivalent (*phi* 108); it is unclear whether there is any connection with the fact that *phalis* is also attested in Pausanias as the title of a priestess of Hera at Argos. Dioscorides notes as well that cannabis was sometimes called "domesticated" or "tame" cannabis (*hêmeros*) to distinguish it from another medicinal plant now identified as hemp mallow (*Althaea kannabina*); this was called, in Greek, either *hydrastina* or "wild" cannabis (*agria*) and, in Latin, "terminal" (*terminalis*; this use of *terminalis* is not attested in any Latin source or recognized by any Latin dictionary, probably because we know it only from the Greek writer Dioscorides; it perhaps reflects a tendency of the plant to grow along paths and hedges and other borders [*termini*], as noted in the *Herbarium* of ps.-Apuleius, 106). Although "wild" cannabis will not be discussed

in this paper, a few of the several ancient references to its medical use are included in Appendix I on the grounds that some ancient medical writers, especially Pliny the Elder, make otherwise unsupported claims about the medical use of "tame" cannabis that closely resemble well-attested uses of "wild" cannabis.

In general, cannabis was a completely uncontroversial element of everyday life for both the Greeks and the Romans, used to make mats, shoes, cloth, and above all ropes. The Romans especially favored hemp for the rope in hunting nets; among the Greeks, on the other hand, it was more often used to make the nautical ropes called *kaloi,* used for furling or "rolling up" the sails and hence known, in English, as "reefing-ropes."

Medically, it was used to treat horses as well as humans; the evidence for its veterinary use is summarized in Appendix II. In the treatment of humans, it was part of the physician's armamentarium, though no more so than a host of other plants. Several parts of the plant could be used. Pliny mentions using the uncooked root on burns, but he may have been thinking of "wild" cannabis here. Another source has cannabis ash used in a poultice, but does not say which part of the plant was burned to produce it. Fresh leaves were used to dress horses' sores, dried ones against nosebleed. But it is the seeds whose use is attested most often, both "green" and mature, distinguished in Greek as *karpos* ("fruit") and *sperma* ("seed").

Before beginning the survey proper, it is just as well to note where cannabis does *not* appear in our ancient medical texts.

First of all, though the medical use of cannabis is recorded in the encyclopedia of Pliny the Elder (written in the middle of the 1st century CE), it is absent from the medical writings of another contemporary encyclopedist, A. Cornelius Celsus (first half of the 1st century), and it seems to be mentioned elsewhere in Latin only in late authors who for the most part translated directly from Greek, such as Marcellus Empiricus (5th century CE) and pseudo-Theodorus (6th century CE?). Hence there is nothing to show conclusively that it was used medically by the Romans, though given the scarcity of evidence I would be reluctant to say that no Roman was ever treated with it; it is conceivable, for example, that when a late Roman authority like Marcellus cites an otherwise unattested use of cannabis, it comes from Roman folk-medicine.

Second, the medical use of cannabis is absent from the works of gynecologists like Soranus (2nd century CE), though this does not necessarily prove that it was never used in treating women. In fact, though one of the principal uses of cannabis seed is one that seems to us to be logically applicable only to males, Aëtius (6th century CE) says that it could be used on women as well. Perhaps the most we can say is that it seems not to have been used for any condition specific to women.

Third, medical cannabis is absent from the writings of Hippocrates (5th century BCE) and his followers, known collectively as the Hippocratic Corpus, though we need not infer that he rejected its use: despite its eventual ubiquity in the classical world, cannabis was evidently unknown to the Greeks before the 5th century BCE, and so Hippocrates' silence may well represent ignorance, not conscious rejection, though absolute certainty is of course impossible.

Cannabis first appears in Greek literature in the celebrated passage where the historian Herodotus, an approximate contemporary of Hippocrates, describes how the ancient Scythians used to toss cannabis seeds onto red-hot rocks and inhale the vapors that were released (4.73-75). Since Herodotus is not concerned with the medical use of the plant, there is, strictly speaking, no reason to discuss the passage at length here; but Brunner (1973, pp. 345-347) discusses it, and the archaeological discoveries alluded to there in n. 45 require some rethinking of what Herodotus described, especially since modern retellings of Herodotus' account continue to abound in inaccuracies and fanciful inventions: Emboden (1972, p. 223) for example, has the Scythians using rocks from funeral pyres, and claims that Herodotus describes them dancing and singing in response.

It should be remembered that cannabis seeds were used by the Scythians not recreationally but as a part of their death-ritual: instead of a wake, they put the corpse of the deceased into a wagon, and for forty days took it on visits to the homes of friends and kin, where it was served at table along with the other guests. It was at the end of this period of mourning that men resorted to the hemp-baths as a form of cleansing (the head being washed first with soap), while the women pursued a different treatment (they smeared a paste of cypress, cedar, and frankincense on their bodies and allowed it stand for a day; when removed, it left their skin fragrant, clean, and shiny).

The nature of the ritual is relevant to the interpretation of the words with which Herodotus describes how the Scythians reacted to the vapor from the seeds, *agamenoi ôruontai*, which are often translated as "[they] howl with delight" or the like. The onomatopoetic verb *ôruontai* certainly describes howling and is used, for example, to describe the sound of wolves (*LSJ* [H.G. Liddell, R. Scott, H.S. Jones, *A Greek-English Lexikon* (Oxford 1968)] *s.v.* "*howl*, prop. of wolves and dogs"); the most recent translation of Herodotus (by R. Waterfield [Oxford 1998]) is therefore certainly wrong to use "shriek." As to the participle *agamenoi*, which describes the state of mind in which the Scythians do their howling, this is invariably translated as "with delight," "with pleasure," or the like; but *LSJ, s.v. ôrumomai*, offers only this passage when illustrating the sense "to howl with joy," and in fact it notes that elsewhere in Herodotus it means "to howl in mourning." The latter is closer to what one might expect in a ritual connected with death, and in fact the basic

meaning of the verb *agamai* is "to be amazed" or "astounded," perhaps expressing here a state of stupefaction. The currently favoured translation may reflect a modern expectation that those who inhale such vapors ought to have a "Reefer Madness" experience and become hysterical, but hilarity conflicts with the fundamentally solemn nature of the experience.

The archaeological discoveries affect the interpretation of the "tents" involved. Herodotus notes that "they lean three poles against one another, cover the poles with felted woolen blankets, making sure that they fit together as tightly as possible, and then put red-hot stones from the fire on to a dish which has been placed in the middle of the pole-and-blanket structure" (4.73); subsequently "the Scythians take cannabis seeds, crawl in under the felt blankets, and throw the seeds on to the glowing stones" (trans. Waterfield). Tombs excavated in Russia have yielded not only an example of the brazier on which the stones were placed but two sets of those "tent-poles" as well. Perhaps the most accessible account is Artamonov (1965; p. 239) there is an illustration of objects recovered from one of the tombs, namely a pot containing hemp seeds, a "censer" that would have held the hot rocks onto which the seeds were thrown, and six "sticks" that "formed the frame of an 18-inch-high tent in which the hemp smoke was collected" (caption). Because of their height, however, these poles could never have formed a viable sauna or spirit-lodge, which the Scythians are sometimes thought to have used, and Waterfield's translation is consistent with this, rendering the verb *hypoduô* as "crawl," as the Scythians would have to do in order to insert their heads into such a structure at ground level.

Since Herodotus' account shows that the Greeks were already familiar with vapor-baths (he states at 4.75 that the seeds release a vapor which no Greek vapor-bath could surpass), it should not be surprising that some of them may have adopted the Scythian habit of using hemp-seed there; that much at least can be inferred from the fact that Hesychius' lexicon (*kappa* 673) records a verb *kannabisthênai* ("to get cannabissed," in effect), defined as "to grow sweaty and hot from the effect of cannabis." It is striking, however, that this definition makes no reference to the cannabis "seizing the head" (the standard euphemism for intoxication), though this just might be subsumed under "to grow hot," since we will see that cannabis seed (eaten, however, rather than inhaled in vapor form) was thought to have a "warming" effect on the body.

Apart from Herodotus, the evidence for Greek familiarity with cannabis in the late 5th and early 4th centuries BCE is ambiguous, consisting of somewhat later scholarly notes that identify certain objects mentioned in comedies of Aristophanes as made from hemp (see the scholia [ancient scholarly notes] to Aristophanes, *Acharnians* 181, *Knights* 129 and 954, *Wasps* 394, and *Plutus* 268); these interpretations, however, may be nothing more than ahistorical as-

sumptions by scholars who lived in a world where hemp products were ubiquitous.

But by about the middle of the 4th century BCE we have evidence for a new use of cannabis seeds, their consumption as a food. Fr. 13 of the comic poet Ephippus constitutes a list of *tragêmata* or "snacks" consumed while drinking at a symposium (the ancient equivalent of the modern Greek *mezedhes*), including *kannabides*. This is a plural form, though probably not (as always assumed) of *kánnabis*, accented on the first syllable and supposedly designating cannabis seed here (though the seed is elsewhere called *karpos* or *sperma*), but of *kannabís*, accented on the last syllable and designating a confection of cannabis seeds and honey. Lexica of ancient Greek do not recognize the existence of *kannabís* = "cannabis-seed cake," but the other foods in Ephippus' list are prepared rather than raw, and *kannabís* in this sense would have the same relationship to *kannabos* (an alternative form of *kannabís*) that *sesamís*, meaning "sesame-seed cake," has to *sésamos*, meaning "sesame-seed."

We will encounter this recreational consumption of the seeds again in the physician Galen, who confirms that they were enjoyed for their psychoactive effect.

We cannot tell when the medical use of cannabis began; since, as far as we can see, the Greeks were eating the seeds before they were using them medicinally, it was perhaps inspired by observations regarding the physiological effects of that consumption. Whenever it began, it was evidently well established by the time of our earliest references to it, which come in the 1st century CE.

Probably the earliest surviving account of the medical use of cannabis is the entry in the *Materia medica* of the Greek physician Dioscorides, published around 65 CE, followed closely by the one in the *Historia naturalis* of Pliny the Elder, finished in 77 CE and dedicated to the emperor Titus. Despite the likelihood that Dioscorides deserves priority, I shall begin with Pliny; he is the only classical Roman writer to discuss the medical use of cannabis, and he lists more medical uses than anyone else, though he is sometimes in conflict with other authorities.

Pliny's *Historia naturalis* has two substantial entries for hemp, one concerned principally with its use in making rope (Pliny the Elder 1967, 19.273-274), the other on its medical use (Pliny the Elder 1967, 20.259):

> Cannabis in siluis primum nata est, nigrior foliis et asperior. semen eius extinguere genituram uirorum dicitur. sucus ex eo uermiculos aurium et quodcumque intrauerit eicit, sed cum dolore capitis, tantaque uis ei est, ut aquae infusus coagulare eam dicatur; et ideo iumentorum aluo succurrit potus in aqua. radix articulos contractos emollit in aqua cocta, item

> podagras et similes impetus; ambustis cruda inlinitur, sed saepius mutatur priusquam arescat.
>
> Cannabis, rather dark and rough in respect to its leaves, first grew in the forests. Its seed is said to extinguish men's semen. A liquid from this casts out ear-worms and whatever animal has entered, but with a headache, and its force is so strong that it is said to coagulate water when poured into it; and so it is good for farm-animals' bellies when drunk in water. Cooked in water, the root softens contracted joints, likewise gouts and similar attacks; uncooked it is spread on burns, but is changed rather often before it dries out.

As can be seen from passage A in Appendix I, Pliny's description of the original plant as dark and rough of leaf resembles Dioscorides' description of "wild" cannabis as having darker and rougher leaves than "tame." Perhaps this reflects a belief that "tame" cannabis had been bred from "wild" cannabis (Herodotus already distinguishes between cultivated and wild varieties of the plant known to the Scythians); or perhaps–and not for the last time–Pliny confused the two plants or carelessly ignored the distinction.

Whether or not this is the earliest surviving account of Greco-Roman medical cannabis, it is certainly our single fullest catalogue of medical uses, though Pliny is explicit about the nature of only four of the five treatments that he records:

1. The use of the seeds: Pliny does not say how the seeds were used, nor is he explicit about why. His comment that they "extinguish the semen" recalls modern claims about reductions in sperm levels in frequent users (cf. Brunner 1973, pp. 349, 351 [with n. 33], and 353); but if the same phenomenon is indeed involved in both cases, one wonders just how the ancients were able to make such an observation. Brunner (1973, p. 349) interprets this and similar ancient comments as references to impotence; it is more likely, however, that they reflect a belief that the seeds have a "drying" quality (as that was understood in ancient physiology), and a passage in Aëtius will show us what appears to have been the main medical purpose of the seeds, which was precisely to "dry up" leaking semen.
2. Its use in treating the ears: Pliny refers to a *sucus* made from the seed that was used to clear vermin out of the ears. Unfortunately, *sucus* is a term of wide application that in a context like this one could designate either a natural juice like sap or a prepared potion. Logically, however, Pliny ought to be referring to the same thing as the *khylos* named in our Greek sources (discussed below) as a treatment for the ears, but no Greek writer has this *khylos* being used against "ear-worms." These vermin were perhaps first mentioned by the satirist Lucilius (2nd century BCE),

but they seem to have been a particular problem in the early Empire, since Pliny records three other remedies for them (Pliny the Elder 1967, 20.256; 23.85; 28.65). Instead, Dioscorides and Galen say that the *khylos* was used for treating pains and inflammations associated with the ears. This is the first–and certainly not the last–time that we must question whether we can take Pliny at his word and assume that he has tapped into a medical tradition not attested in our other sources, or whether he was mistaken because he had difficulty in understanding a Greek source, used defective texts of Greek medical writers, or was simply confused. In fact, there is a second example of this same dilemma here, since headaches, which Pliny ascribes to the use of this *sucus* in the ears, are elsewhere associated with eating the seeds.

3. This *sucus* as a remedy for the "bellies" of farm-animals: If Pliny means that it was used to prevent or control diarrhea (a Latin word meaning "therefore" connects this reference to the ability to coagulate water), this is another use known to him alone. If, on the other hand, he is alluding to the seed-based remedy for tapeworms attested in the treatment of both humans and horses (see below), this remedy does not involve the preparation of a *khylos,* only a combination of chopped seeds and water filtered to remove the grit.
4. The use of the cooked root on joints and against gout: No other medical authority mentions any medical use for the cannabis root; on the other hand, two passages in Dioscorides (passages A and B in Appendix I) refer to a poultice made from the boiled root of *wild* cannabis supposedly effective against inflammations and chalk-stones (*Materia medica*) or against chalk-stones and twisted sinews (*Euporista*).
5. The use of the raw root on burns: No other medical authority mentions any use for the uncooked root of cannabis, but we have recipes (including passage C in Appendix I) for preparations supposedly effective against such eruptions on the head as melicerides (encysted tumors) that use the "dry" root of *wild* cannabis.

Pliny is a source that should be used with the greatest caution; while he provides information that other sources do not, some of his "facts" could be argued to result from confusing different uses of cannabis, or from confusing the medical uses of cannabis and of wild cannabis.

Dioscorides' *Materia medica* is a complete guide to ancient medicines, describing in its botanical section both the appearance and the medical uses of the plants discussed; its entry for cannabis includes more or less the same two points with which Pliny began (Dioscorides 1907-1914, *Materia medica* 3.149.1):

> κάνναβις· φυτὸν εὔχρηστον τῷ βίῳ πρὸς τὰς τῶν εὐτονωτάτων σχοινίων πλοκάς. φύλλα δὲ φέρει παραπλήσια τῇ μελίᾳ, δυσώδη, καυλοὺς μακρούς, κενούς, καρπὸν στρογγύλον, ἐσθιόμενον, ὃς πλείων βρωθεὶς σβέννυσι γονήν· χλωρὸς δὲ χυλισθεὶς ἁρμόζει πρὸς τὰς τῶν ὤτων ἀλγηδόνας ἐνσταζόμενος.
>
> Cannabis: A plant useful for life on account of the twisting of well-strung ropes. It bears foul-smelling leaves resembling the ash, large hollow stems, a round fruit which is eaten, and when consumed in quantity extinguishes the semen; if infused when green, it is suitable for instilling against ear-aches.

Dioscorides perhaps described the leaves more clearly in another work, when he wrote of the leaves of the eupatorion that they "are set at a distance and strongly split into 5 or more parts, looking much like those of the cinquefoil or cannabis" (Dioscorides 1907-1914, *Materia medica* 4.41; much the same information is provided by Pliny the Elder 1967, 25.65 and Oribasius 1933, *Collectiones medicae* 11.*epsilon*.20).

Though he too seems not to be explicit about the medical use of the seeds, Dioscorides records the valuable information, absent from Pliny's account, that they affected the body as a result of being eaten and that they had to be consumed in substantial quantities to produce the drying effect.

With regard to the treatment for earaches, Dioscorides specifies that the seeds were prepared while still green and immature. The participle *khylistheis,* translated above as "infused," shows that they were subjected to the process called *khylismos,* which resulted in a *khylos,* a juice combining substances from both the seeds and the liquid in which they were infused; such a *khylos* made from green cannabis seed is mentioned in another work of Dioscorides (Dioscorides 1907-1914, *Euporista* 1.54) as one of several preparations effective against "pains and inflammations around the ears" if instilled while warm.

Brunner (1973, pp. 350 and 353) understands the liquid used in the ears as "seed-juice," but pressing the seeds would surely yield oil rather than "juice." According to *LSJ*, *khylizô* means to extract juice from a plant through either infusion or decoction, but an examination of Dioscorides' actual usage reveals that the process involved only infusion, not decoction. It was evidently common enough to be mentioned well over 100 times in the *Materia medica* alone, and it was normally applied to plants (there is an entire section on how to *khylizein* dry botanical material), though there is also one formula for asses' dung infused in wine as a remedy against scorpion-bites. The plant might be worked whole, root and all, or only one part might be used (roots, stalks, grasses, leaves, and seeds are all attested explicitly), or some combination of two or more of these. Whatever was being processed was first prepared, almost

always by chopping, though there are a few references to preparing roots by bruising. To this a liquid would then be added. One recipe suggests water or wine, another rain water or old wine; other liquids mentioned include warm water, *passum* (a very sweet wine made from raisins), oxymel (a combination of vinegar and honey), and honey-wine or mead (mentioned three times, twice as *melikraton*, once as *hydromel*). A period of steeping presumably followed in all cases, though it is mentioned explicitly only a few times, and only two recipes specify the length (5 days in both cases; two others say "sufficient days"). This steeping did not involve the application of heat; a few formulas in the *Materia medica* specify a period of boiling, but it always follows the steeping (hence the inappropriateness of "decoction" as a translation of *khylos*). After steeping (and sometimes boiling), the plant material would be strained (a strainer is mentioned once) or squeezed in a press (again mentioned only once, but its use was presumably standard) to extract the liquid, which constituted the *khylos*. While the creation of this liquid was obviously the goal with cannabis seed and with some of the other formulas, in other cases the goal was instead to transform the plant material itself, which would subsequently be dried, sometimes in sun, sometimes in shade, before use, while the *khylos* would apparently be discarded (if not already boiled away). Thus the preparation that was warmed and instilled into the ear against inflammations and pains would have been produced by chopping green cannabis seeds, soaking them for a period in water or some mildly alcoholic liquid such as wine, and finally pressing out the fluid. If this is indeed the same as the *sucus* mentioned by Pliny as having the ability to "coagulate" water, then uncertainties about the liquid used to produce it make it difficult to comment on the speculation offered at Brunner (1973, p. 353).

The medical use of cannabis continues to be well attested in the second century CE in the writings of the Greek physician Galen. His work *De simplicium medicamentorum temperamentis et facultatibus* ("On the temperaments and properties of simple medications") offers an evaluation of the utility of the seeds which again begins with the very same two points made by Pliny and Dioscorides (Galen 1821, XII.8):

> Καννάβεως ὁ καρπὸς ἄφυσός τε καὶ ξηραντικὸς εἰς τοσοῦτόν ἐστιν ὡς, εἰ πλείων βρωθείη, ξηραίνειν τὴν γονήν. ἔνιοι δὲ χλωρὸν αὐτὸν χυλίζοντες εἰς ὤτων ἀλγήματα χρῶνται τὰ κατ' ἔμφραξιν, ὡς ἐμοὶ δοκεῖ, γινόμενα.

> The fruit of cannabis is both non-flatulent and drying to such an extent that, if consumed in quantity, it dries up the semen. Some make an infusion of it while green and use this against those ear-aches, I believe, that occur through blockage.

In terms of treatment, the novelty here is the acknowledgement that the infusion works specifically against ear-aches caused by blockage; though (unlike Dioscorides) he does not remark that it was used warm, could Galen have realized that the *khylos* was effective simply because, like any other warm liquid, it could dislodge ear wax? Another novelty here is our first reference to the anti-flatulent quality of the seeds; a later writer notes that this property is so strong that, if cannabis seeds have been eaten, there is no flatulence even after eating foods that cause it (Oribasius 1933, *Synopsis* 4.21, "the fruit of cannabis is non-flatulent even after flatulent foods"). Brunner (1973, p. 350) has the ambiguous translation "eliminates intestinal gas": "prevents" would be more precise.

Galen's account also puts the use of cannabis seeds within the context of ancient medical theory. Health was dependent not only upon the proper balance of the four humors black bile, yellow bile, blood, and phlegm but also upon the proper balance of the four qualities of warm, cold, dry, and moist; indeed, it could be influenced through the consumption of or abstention from those foods and medications that inherently possess these qualities or enhance them in the body. Hence we can see for the first time a connection between the drying up of semen through high-level consumption of the seeds and a supposed "drying" quality inherent in the seed (see also Hesychius' lexicon [*kappa* 764], which defines cannabis as a Scythian *thumiama* [i.e., incense] that has the ability to "dry out" everyone in the vicinity).

Since many ancient medications were, as we now say, "natural-source" and were in fact everyday foods as well, Galen also wrote about the eating of mature cannabis seed in another work called *De alimentorum facultatibus*, "On the properties of foods" (Galen 1821, VI.549):

> Περὶ καννάβεως σπέρματος.
> Οὐχ ὥσπερ αὐτὸ τὸ φυτὸν τῆς καννάβεως ἔοικε πως τῷ ἄγνῳ, καὶ τὸ σπέρμα τῷ σπέρματι παραπλήσιόν πώς ἐστι τὴν δύναμιν, ἀλλ' ἀποκεχώρηκε πάμπολυ, δύσπεπτόν τε καὶ κακοστόμαχον ὂν καὶ κεφαλαλγὲς καὶ κακόχυμον. ὅμως δ' οὖν καὶ τοῦτό τινες ἐσθίουσι φρύγοντες ἅμα τοῖς ἄλλοις τραγήμασιν. ὀνομάζω δὲ δηλονότι τραγήματα τὰ παρὰ τὸ δεῖπνον ἐσθιόμενα τῆς ἐπὶ τῷ πίνειν ἡδονῆς ἕνεκα. θερμαίνει δ' ἱκανῶς καὶ διὰ τοῦτο καὶ κεφαλῆς ἅπτεται βραχεῖ πλεῖον ληφθέν, ἀτμὸν ἀναπέμπων ἐπ' αὐτὴν θερμόν θ' ἅμα καὶ φαρμακώδη.

> On the seed of cannabis:
>
> While the cannabis-plant itself resembles to a degree the agnus plant, the seed is not at all like its seed in its power but completely different, being

> both hard to digest and tough on the stomach and headache-inducing and bad-tasting. All the same, however, some people eat it, munching on it together with other snacks. By 'snacks' I mean the things eaten at dinner on account of the pleasure associated with drinking. It warms sufficiently, and for that reason it also intoxicates quickly when eaten in quantity by sending toward the head a vapor that is both warm and medicinal.

The word translated "vapor" here (*atmos*) is another form of the one used by Herodotus to describe what was released when the Scythians threw cannabis seed onto the hot rocks (*atmis*). The word translated "medicinal" here is rendered by Brunner 1973, p. 350 as "toxic," but *pharmakôdês* simply means "of the nature of a *pharmakon*" (*LSJ s.v.*), while *pharmakon* itself designates a "*drug*, whether healing or noxious" (*LSJ s.v.*); since "drug-like" could be misleading in the context of treatment with cannabis, I have chosen "medicinal."

Again the influence of contemporary theory is evident in the reference to the "warming" quality of cannabis, naturally associated with its "drying" quality; this probably alludes not to a "warm" feeling felt by the user (Brunner 1973, p. 351) but to the ability of the seed to maintain the body's warmth, the prerequisite of life. But this passage also constitutes our best evidence for the recreational use of cannabis through consumption of the seeds (denied at Brunner 1973, p. 355), which we last saw mentioned in Ephippus in the 4th century BCE: surely it was for the intoxicating effect, and not for the unpleasant taste or for the stomachaches or headaches, that they were eaten. Galen confirms this intoxicating effect a little later in the same work (Galen 1821, VI.550) when he writes that the seed of agnus-castus doesn't "touch the head" as cannabis seed does.

One "paramedical" use worth mentioning is as a mosquito repellent (cf. Brunner 1973, p. 349). An ancient work on farming claims that "with cannabis spread below, mosquitoes will do no injustice to the one in the bed" ([Anon.] 1895, *Geoponica* 13.11.9), while elsewhere it promises that "if you put a blooming sprig of fresh cannabis by you when going to bed, mosquitoes won't touch you" ([Anon.] 1895, *Geoponica* 13.11.4). Whether or not these actually work, they might reflect an observation by ancient hemp-farmers that insects by and large tend to avoid the plant.

A work falsely attributed to Galen called *De remediis parabilibus* ("On ready remedies") offers cannabis leaves in a treatment against nose-bleeds (Galen 1821, XIV.548): "Dry some cannabis leaves, grind them and put them into the *rhothôn*" (the suggested alternative is to set fire to a piece of linen, dip it in "sharp vinegar," and insert it into the nostril!). Unfortunately, *rhothôn*

does not occur elsewhere and is not found in any Greek dictionary I have consulted, but one assumes that it designates the nostrils.

Cannabis seed appears twice in remedies for tapeworms. One that is also attested for horses (see Appendix II) turns up in "On ready remedies" (*Opera omnia* XIV.515):

> Καννάβεως σπέρμα ξηρὸν κόψας καὶ σήσας, ὕδατι μίξας καὶ χυλώδες ποιήσας καὶ ῥάκει καθαρῷ ἀποπιάσας δὸς πιεῖν.

> Chop and sift dry cannabis seed, mix with water and make *khylos*-like, and press through a clean rag and administer.

As *sperma* shows, this involves mature seed rather than the green seed used to make the *khylos* for earaches; it is not clear, however, what the author meant by "*khylos*-like" (a brief period of steeping before filtering?). Archigenes fr. 17 offers the second recipe, involving a drink prepared from a number of seeds, including cannabis.

Greek medicine as a form of scholarly inquiry effectively ended with Galen, and later writers, for the most part, simply rehash and recycle what we have already found.

In the 4th century, Oribasius repeats in one passage (Oribasius 1933, *Ad Eunapium* 2.1) what Galen says in "On the temperaments and properties of simple medications" about the seed drying up the semen; in another (Oribasius 1933, *Collectiones medicae* 1.32) he abbreviates Galen's comments in "On the properties of foods" about their indigestible quality and their warming effect. In the 6th century, Aëtius writes as follows (Aëtius 1935, *Iatrica* 1.178):

> Καννάβεως ὁ καρπὸς δύσπεπτός τέ ἐστι καὶ κεφαλαλγὴς καὶ κακόχυμος· εἰ δὲ καὶ φρυχθείη καὶ οὕτως ἅπτεται τῆς κεφαλῆς τῷ θερμαίνειν ἱκανῶς, ἀτμὸν ἀναπέμπων ἐπ' αὐτὴν θερμόν τε ἅμα καὶ φαρμακώδη· τῷ δὲ ξηρὰν ἔχειν τὴν κρᾶσιν καὶ ἄφυσον εἶναι ξηραίνει τὴν γονήν.

> The fruit of cannabis is hard to digest, headache-inducing, and bad-tasting; even if it is roasted it intoxicates by warming the head sufficiently, sending up a warm medicinal vapor toward it; by having a dry and non-flatulent temperament it dries the semen.

This is more or less what Galen wrote in "On the properties of foods," but perhaps a little confused; the explicit connection made here between the

non-flatulent property of the seed and its ability to dry may be based upon a misunderstanding of Galen and his use of "both . . . and" (Galen probably meant that the seed was, on the one hand, non-flatulent and, on the other, drying to such an extent that it dried up the semen, not that both the non-flatulent and drying properties dried up the semen). Finally, in the seventh century, Paulus of Aegina (Paulus Aegineta 1921-1924, *Epitome medica* 7.3.10) repeats more or less word for word the comments from Galen's work "On the temperaments and properties of simple medications." Late Roman writers like Marcellus Empiricus and pseudo-Theodorus closely reflect what we have already seen in Greek writers, though they sometimes add an outlandish novelty or two (cf. Brunner 1973, p. 354).

Outside these specific accounts, cannabis seed regularly appears in lists of foods with various qualities: non-flatulent foods (Oribasius 1933, *Collectiones medicae* 3.22.1, 15.1:10.9, *Synopsis ad Eustathium filium* 4.21.2, *Ad Eunapium* 1.38.1; Aëtius 1935, *Iatrica* 2.258), foods with a drying effect (Oribasius 1933, *Collectiones medicae* 14.23.1, 15.1:10.9, *Synopsis ad Eustathium filium* 2.13.1; Aëtius 1935, *Iatrica* 2.209), foods with a warming effect (Oribasius 1933, *Collectiones medicae* 3.31.2, *Synopsis ad Eustathium filium* 4.31.2), and foods that harm the head (perhaps because of the headaches said to be associated with eating it; [[Anon.] 1841] *De alimentis* 31, under the designation *kannabokokka*; Oribasius 1933, *Collectiones medicae* 3.21.3, *Synopsis ad Eustathium filium* 4.20.1). Some writers also record it as a powerful thinning agent, i.e., as having the ability to thin the body's humors (Oribasius 1933, *Collectiones medicae* 3.2.4 = *Synopsis ad Eustathium filium* 4.1.3 = *Ad Eunapium* 1.18.3, "among agents that thin powerfully enough to be medicinal is the seed of rue and of cannabis"; Aëtius 1935, *Iatrica* 2.240 gives a substantially identical text). Under the compound name *kannabosperma* ("cannabiseed," as it were), it also appears once in a list of foods that produce "sticky" humors ([Anon.] 1840 *De cibis* 18), specifically in a sub-list of foods that also produce "cool" humors.

The imitative quality of later Greek medical writing has one advantage for us: that later writers can sometimes preserve knowledge that has otherwise been lost. In the case of cannabis seed, though we have seen numerous references to the ability of the seed to suppress semen when consumed in quantity, we have seen none that has related this explicitly to a medical use. Fortunately, a passage of Aëtius on the treatment of "gonorrheas" or involuntary discharges of sperm shows us the medical use that exploited that drying effect (Aëtius 1935, *Iatrica* 11.33):

Γονόρροια μὲν οὖν τῶν σπερματικῶν ἀγγείων ἐστὶ πάθος, οὐ τοῦ αἰδοίου. ὀδύνην μὲν οὐκ εἴωθε λίαν ἐργάζεσθαι τὸ πάθος, ἀειδίαν δὲ οὐ τὴν τυχοῦσαν καὶ συγχυσμὸν παρέχει, ἀδιαλείπτως ἐκκρινομένου τοῦ σπέρματος ἀπροαιρέτως. Ἀποτελεῖται δὲ ἐνίοτε καὶ ἐκ ῥευματισμοῦ τῶν σπερματικῶν ἀγγείων, ἔστι δὲ ὅτε καὶ σατυριάσεως προηγησαμένης ἐπιγίγνεται ἡ γονόρροια. Συμβαίνει δὲ τὸ πάθος τοῖς προηβῶσι μᾶλλον, τοῖς περὶ τὸ τεσσαρεσκαιδέκατον ἔτος· ἤδη δὲ καὶ ταῖς ἄλλαις ἡλικίαις. Ἔστι δὲ τὸ ἐκκρινόμενον σπέρμα ὑδαρὲς λεπτὸν δίχα προθυμίας τῆς περὶ τὴν συνουσίαν, τὰ πλεῖστα μὲν ἀναισθήτως, ἔστι δὲ ὅτε καὶ μετά τινος ἡδονῆς· καταφθείρεται δὲ αὐτοῖς ἠρέμα τὸ σύμπαν σῶμα ἰσχαινόμενον, ἰδίως δὲ τὰ κατὰ τὴν ὀσφύν. Παρέπεται δὲ καὶ ἀτονία πολλή, οὐ διὰ τὸ πλῆθος τοῦ ἐκκρινομένου, ἀλλὰ διὰ τὴν κυριότητα τῶν τόπων. Οὐ μόνον δὲ ἀνδράσιν, ἀλλὰ καὶ γυναιξὶ τοῦτο συμβαίνει, καὶ ἔστιν ἐπὶ τῶν γυναικῶν δυσαπάλλακτον. Θεραπεία δὲ καὶ τούτων κοινὴ ἡ ἐπὶ παντὸς ῥευματισμοῦ παραλαμβανομένη. Πρῶτον μὲν οὖν ἐπὶ ἡσυχίας καὶ ὀλιγοσιτίας καὶ ὑδροποσίας τηρεῖν· εἶτα δὲ καὶ σκέπειν τὴν ὀσφὺν καὶ τὸ ἐφήβαιον ἐρίοις βεβρεγμένοις οἴνῳ καὶ ῥοδίνῳ ἢ οἰνανθίνῳ ἢ μηλίνῳ· οὐκ ἄθετοι δὲ οὐδὲ σπόγγοι, ὀξυκράτῳ δεδευμένοι· ταῖς δὲ ἑξῆς καὶ καταπλάσμασι τοῖς διὰ φοινίκων, μήλων, ἀκακίας, ὑποκιστίδος, οἰνάνθης, ῥοὸς ἐρυθροῦ, καὶ τῶν ὁμοίων, ἐγκαθίσμασί τε χρῆσθαι στυπτικοῖς, ἀφεψήμασι σχίνου, βάτου, μυρσίνης καὶ τῶν παραπλησίων, ἑψομένων ἐν οἴνῳ αὐστηρῷ ἢ ἀκράτῳ ἢ κεκραμένῳ. Τροφαῖς δὲ χρῆσθαι δυσφθάρτοις τε καὶ δυσμεταβλήτοις καὶ ἀναξηραντικαῖς, διδόναι τε αὐτοῖς σὺν τῷ ποτῷ καὶ ταῖς τροφαῖς τοῦ ἄγνου τὸ σπέρμα καὶ τὸ τῆς καννάβεως, καὶ μᾶλλον πεφρυγμένα, καὶ τοῦ πηγάνου τὸ σπέρμα καὶ τὰ φύλλα, καὶ τῆς θριδακίνης τὸ σπέρμα καὶ τοὺς καυλούς, καὶ τῆς νυμφαίας τὴν ῥίζαν. Πίνειν δὲ κατὰ ἑκάστην ἡμέραν ἀντὶ τοῦ κοινοῦ ὕδατος ὕδωρ ἐν ᾧ σίδηρος πλειστάκις ἐναπεσβέσθη. Ἔδωκαν δέ τινες τοῖς γονορροικοῖς πίνειν ἁλικακκάβου ῥίζης τὸν φλοιὸν μετὰ ὕδατος, καὶ οὐκ ἂν εἴη ἀνοίκειον ἀποπειρᾶσθαί ποτε καὶ τούτου.

So a gonorrhea is a condition of the spermatic ducts, not of the penis. The condition generally does not cause much pain, but it does offer an unusual deformity and effusion, as the seed is incessantly being discharged involuntarily. Sometimes a gonorrhea is brought about by a discharge of the spermatic ducts, sometimes it is an aftereffect of a preceding satyriasis. The condition happens most to the young, around the age of fourteen, though at other ages as well. The seed is discharged in a watery and thin condition, unconnected with any desire for sex, mostly without being no-

> ticed, though sometimes with a certain pleasurable sensation. The entire body, but especially the areas around the loin, is gradually wasted and withered by it. Significant weakness follows, not because of the quantity of the discharge but because of the sovereignty of these areas. This happens not only to men but to women as well, and in the case of women it is difficult to cure. The general treatment of these conditions is the one for every kind of discharge. First of all, then, keep the patient rested, eating little and drinking only water; then also cover the loin and pubes with wool moistened with wine and attar of rose or grape-bloom or quince (sponges dipped in diluted sour wine are not to be rejected); in the days that follow use poultices from dates, quinces, acacia, hypocist, grape-bloom, red sumach and the like, and astringent sitz-baths, decoctions of mastich, bramble, myrtle and similar things, boiled in dry wine, either unmixed or mixed. Use foods that are hard to digest and assimilate and are drying, and give to them together with the drink and food the seed of agnus-castus and of cannabis, preferably roasted, and the seed and leaves of rue, as well as the seed and stalks of wild lettuce and the root of the water-lily. Every day, instead of ordinary water, some give water in which steel has been quenched often, some the bark from the root of the winter-cherry.

Despite the comment that this "affliction" can occur in women as well (perhaps Aëtius was thinking of vaginal secretions, though they are obviously–to us, at least–not discharges of semen), it is clear that Aëtius is discussing principally wet-dreams and nocturnal emissions in teenage boys. This phenomenon evidently caused great concern to ancient physicians; the passage quoted above is not even the whole of Aëtius' discussion of its treatment, but one can see that it involves plenty of rest, a restricted intake of food, and abstention from beverages other than water (obviously the physicians who administered water from the blacksmith's that had been used for quenching hot steel were engaging unconsciously in a sort of homoeopathic magic). But the logic of Aëtius' treatment is inescapable: these discharges represent leakage from the spermatic ducts, and so the drying quality of cannabis seed can be invoked to dry up those leaks.

A passage in Oribasius (Oribasius 1933, *Ad Eunapium* 4.107.2) has the fruit of "wild" cannabis used in this treatment, but he is very probably mistaken; his language reflects exactly what other authorities say about the effect of cannabis seed ("if drunk in quantity it dries up the semen"), and no other medical authority except the *Herbarium* of ps.-Apuleius refers to any use at all for the seed of "wild" cannabis. That Oribasius writes of the fruit being "drunk" rather than eaten is also likely to be an error, unless he was simply thinking about the seeds being taken together with a beverage.

This survey of the medical use of cannabis has yielded several weakly attested uses: a preparation of dry seed against tapeworms, the dried, ground leaves against nosebleed. But it has also shown that there were two principal uses, attested again and again in our major medical authorities: an infusion of the green seeds used against earaches, and consumption of the seeds in treating nocturnal emissions. For a variety of reasons, it is difficult to evaluate the effectiveness of these treatments, most obviously because of the impossibility of experimenting with the precise strains that were used in antiquity, less obviously because we cannot always be certain about the method of preparation (for example, no-one tells us whether the *khylos* used in the ears was prepared with water, with wine, or even with oxymel). It may well be, however, that the lack of a technology to permit smoking cannabis meant that the ancients were denied the opportunity to make the most effective use of the plant's psychoactive and analgesic properties.

Finally, one section of a genuine work of Galen, *De victu attenuante* ("On the thinning regimen," Galen 1923, 29), hints at some controversy over the medical use of cannabis seed. Galen is making the point that some foods exercise such a powerful effect on the body that they are little short of the properties of true medicines. His first example is the seed of the rue, followed by the seed of the agnus-castus (which we've seen associated elsewhere with the medical use of cannabis), followed by cannabis seed, which he says is not only medicinal but also headache-inducing, so that "one would properly use them [i.e., the seeds of these three plants] for only one purpose, when one chooses to purify the blood through the urine." Since no other source connects cannabis seed with purification of the blood (or with the urine), it is not clear what Galen had in mind here. What does seem certain is that his words reflect a perception that there was such a thing as an *improper* use for the seed. It seems unlikely that Galen was thinking of the poorly attested use of cannabis seeds against tapeworms or even of the much better attested use of a *khylos* from them against earaches. In the absence of any other attested medical use of cannabis, this leaves the drying up of semen as his most likely target; since we know that Galen was aware that eating the seeds was not only unpleasant but could lead to intoxication as well, it is perhaps not unreasonable to suspect that the controversy underlying his words was precisely over the prescribing of cannabis seeds for the treatment of nocturnal emissions in teenage boys, inspired by observations of undesirable side-effects from administering the large quantities of seed that were required to produce the "drying" effect. It is worth noting that, when Aëtius goes on to offer a specific recipe for an antidote to nocturnal emissions, it contains the seed of agnus-castus but not of the more intoxicating cannabis (see Galen, quoted above, for agnus-castus as a non-intoxicating alternative to cannabis).

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APPENDIX I

Passages Discussing "Wild" Cannabis Possibly Misunderstood as Discussing "Domesticated" Cannabis:

A. Dioscorides, *Materia medica* 3.149 (cf. Oribasius, *Collectiones medicae* 11.*kappa*.3):

ἡ δὲ ἀγρία κάνναβις ῥαβδία φέρει ὅμοια τοῖς τῆς πτελέας, μελάντερα δὲ καὶ μικρότερα, τὸ ὕψος πήχεως· τὰ φύλλα ὅμοια τῇ ἡμέρῳ, τραχύτερα δὲ καὶ μελάντερα, ἄνθη ὑπέρυθρα, λυχνίδι ἐμφερῆ, σπέρμα δὲ καὶ ῥίζα ὅμοια τῇ ἀλθαίᾳ. δύναται δὲ ἡ ῥίζα καταπλασθεῖσα ἑφθὴ φλεγμονὰς παρηγορεῖν καὶ πώρους διαχεῖν· καὶ ὁ ἀπ᾽ αὐτῆς δὲ φλοιὸς εὔθετεῖ εἰς πλοκὴν σχοινίων.

Wild cannabis bears shoots similar to those of the elm, but darker and smaller, the height of a forearm; the leaves are like the domesticated variety, but rougher and darker, the flowers reddish, similar to the toad-flax, the seed and root like the wild mallow. The root when boiled and used as a plaster can ease inflammations and disperse chalk-stones; and the inner bark from it serves for making ropes.

B. Dioscorides, *Euporista* 1.229

πώρους δὲ τοὺς ἐπὶ ποδαγρικῶν καὶ συστροφὰς τῶν νεύρων λύει … κάνναβις ἀγρία καταπλασθεῖσα …

Cures for chalk-stones in the gouty and for twistings of the sinews include . . . a plaster of wild cannabis.

C. Oribasius, *Synopsis ad Eustathium filium* 3.29.1 (cf. Aëtius 1935, *Iatrica* 15.7):

᾽Αδαμαντίου πρὸς μελικηρίδας καὶ τὰ ὅμοια
Κηροῦ β′, τερεβινθίνης β′, λεπίδος χαλκοῦ β′, νίτρου α′, θείου ἀπύρου α′, καννάβεως ἀγρίας ῥίζης ξηρᾶς λε′ (εἰ δὲ μή, ἀριστολοχίας στρογγύλης τὸ αὐτό), κόπρου περιστερᾶς λε′, ἐλαίου παλαιοῦ α′. ἐναφέψει τῷ ἐλαίῳ τὰς ῥίζας.

> Adamantius' [remedy] against melicerides and the like:
>
> Two measures of wax, 2 of terebinth, 2 of bronze chips, 1 of nitre, 1 of native sulphur, 35 of dry root of wild cannabis (otherwise the same amount of round aristolochia), 35 of pigeon-droppings, 1 of old oil. Boil down the roots in the oil.

APPENDIX II

Cannabis in Veterinary Medicine

According to a collection of horse-remedies known as the "Berlin *Hippiatrica*" ([Anon.] 1924, 96.26), the chopped leaves can be used to dress a wound: first some vinegar and pitch are brought to a full rolling boil, then wax, mustard, wheat-chaff, and roasted pine-resin are added, and the resulting mixture (presumably cooled) is applied liberally, then chopped cannabis leaves and grass trimmings are put on top before the wound is bound. This treatment evidently does not rely upon any chemical properties of cannabis leaves but simply uses them (no doubt as a waste product from cultivation for rope-making) as a clean and readily available dressing.

Another collection, the "Cambridge *Hippiatrica*," offers a recipe for the treatment of tapeworms which is identical to the one cited above from pseudo-Galen "On ready remedies" ([Anon.] 1924, 70.10).

Finally, a formula found in both the "Cambridge *Hippiatrica*" ([Anon.] 1924, 17.3) and in the *Geoponica* ([Anon.] 1895, *Geoponica* 16.15) specifies the use of the ash of cannabis (though we are not told whether this is from burning the stems or the leaves or even the root) combined with honey and "old urine" as a salve for wounds of the lower back (for the "back-biting" of horses and the use of cannabis to control it, cf. Brunner 1973, p. 354, with n. 40).

A Homelie Herbe: Medicinal Cannabis in Early England

Vivienne Crawford

ABSTRACT. Cannabis is often regarded as a substance alien to British culture until the 1960s, at which supposed point of introduction it functioned as a marker of subversion. In fact cannabis was used as a medicinal herb by the Anglo-Saxons, and highly valued during the Tudor and Stuart periods. It remained in the British *Materia medica* through the 18th and 19th centuries, being well regarded by orthodox doctors. However, the type of cannabis grown in England was probably less rich in psychotropic cannabinoids than plants grown in the East.

KEYWORDS. Anglo-Saxon herbalism, English Renaissance herbalism, cannabis, medicinal marijuana, history of medicine

INTRODUCTION

Although medical herbalism has an ancient and venerable history, its use in Britain since the seventeenth century has increasingly been the subject of contention. This is not a function of the perceived efficacy of plant medicine. Rather, the authorisation or prohibition of particular therapeutic practices re-

Vivienne Crawford is a former lecturer in Renaissance Literature. She holds post-graduate degrees in English and American Literature from Harvard, as well as degrees in Philosophy from University College, London and the University of Canterbury, New Zealand. She recently completed a BSc degree and Clinical Training in Herbal Medicine.

Address correspondence to: Vivienne Crawford, The Cottage, Brearley Old Hall, Luddendenfoot, West Yorkshire HX2 6HS, England.

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flects the fluctuating distribution of power by means of which the civic body, as represented by the government and the professions it recognises and licences, asserts its right to regulate the individual body of the citizen. Legal control has been particularly overt in the case of psychoactive plants such as cannabis, which possess the politically and morally charged property of changing the way we see the world.

Prohibited for common use in Britain since the 1920s, and banned even for prescription by doctors since the 1970s, cannabis is currently the subject of experimentation purporting to prove to the satisfaction of science that the plant is a cornucopia of therapeutic constituents. As in America, orthodox pharmaceutical and medical bodies have been canvassing the government to authorise clinical trials and grant licences for cannabis-based medicines. Transformed almost overnight from outlaw to commercial opportunity, cannabis is the subject of urgent investigation on the part of commercial scientists, as companies on both sides of the Atlantic scramble to patent profitable analogues. I suggest that a rational consideration of its venerable history in England, coupled with the evidence of its therapeutic properties (newly confirmed in the language of biochemistry), leads to the inescapable conclusion that the prohibition of medicinal cannabis in England is an historical anomaly that should be rectified as soon as possible. Indeed, the British government is moving in this direction: cannabis has recently (October 2001) been re-classified in recognition of the fact that by any measure, it is much less dangerous than substances such as street heroin. GW Pharmaceuticals' cannabis-based medicines are in the final stages of U.K. testing. Yet there is no official will to restore cannabis to its former position in the repertory of common herbs available to qualified practitioners, let alone to legalise the growing of the plant for home consumption. Cannabis is still perceived as an alien drug, and despite reports in the popular press about its use as self-medication for pain control, or to ease the effects of neuromuscular dysfunction, one that is primarily associated with an anti-social hedonism.

Trease and Evans (1998) state that cannabis is believed to have reached Europe via Napoleonic Egypt. However, an authoritative 19th-century history of drugs (Flückiger and Hanbury 1879) details the way in which it became prominent in contemporary British medicine following the *in vivo* research carried out by O'Shaughnessy in Calcutta, during the 1830s. Grinspoon (1997) adds that between 1840 and 1900, more than a hundred papers were published on its therapeutic effects.

Whilst this may be accepted as the inauguration of modern usage, hemp had in fact been a staple of indigenous European medicine for more than a millennium. In addition, like its cousin the nettle, cannabis was a source of fibre for rope and cloth. Its seeds provided food, and crushed, yielded oil rich in essential fatty acids to nourish both people and their beasts.

Why then was it seen in the Victorian period as a new plant? Even the reputable Grieves' *Herbal* (Grieve 1971) speaks of cannabis as if it reached England only in the mid-nineteenth century. I believe the answer is that during this period, the strain of cannabis most commonly employed in Britain for both medicinal and psychotropic purposes was the variety known as *Cannabis indica* or Indian hemp, imported from the Indian sub-continent in the form of compressed resin, whereas previously, medicinal use had been made of the leaves, seeds and roots of cannabis plants grown in a northern climate.

There is no absolute consensus as to whether cannabis is a closely related genus of plants, including *Cannabis sativa*, *C. indica*, and *C. ruderalis*, or a single polymorphic species with variant ecotypes, each carrying different proportions of cannabinoid constituents depending on environmental circumstances (Flückiger and Hanbury 1879; Staryk 1983; Schultes and Evans 1992; Trease and Evans 1996; GW Pharmaceuticals website 2001). Whichever is truer, the fact that the Anglo-Saxons do not record any mind-altering effects for their homegrown hemp seems to suggest that 10th-century English-grown cannabis lacked the concentration of sunlight-induced terpenophenolic metabolites (e.g., delta-8 and delta-9 tetrahydrocannabinol, etc.) responsible for changes in consciousness, and consistently present in plants grown in the light and heat of Asia. Either the potentially psychotropic effects of the plant were unknown, or, if occasionally observed, were not regarded as controllable in a therapeutic context, and hence not recorded in reference texts.

Anglo-Saxon and Classical authors simply differentiated *C. sativa* (cultivated) from *C. sylvestris* or *agria* (wild). It has been suggested that the latter is *Eupatorium cannabinum*, but in the *Durham Glossary of the Names of Worts* (Cockayne 1856,Vol. 1 p. 329), *C. agria's* synonym is "holi rope," in my view an epithet applying more properly to cannabis. Reversing the usual route of plant migration, by means of which wild-growing Mediterranean herbs were introduced for cultivation into colder parts of Europe, *C. sativa* came to Greece and Italy from the northeast. Excavation of Western Altaic burial mounds has confirmed the Scythian custom of inhaling the fumes of cannabis seeds, heated in pots or on stones in an enclosed space, described by Herodotus *circa* 500 BCE (*Histories*, bk.IV, p. 295): " . . . it begins to smoke, giving off a vapour unsurpassed by any vapour-bath one could find in Greece. The Scythians enjoy it so much that they howl with pleasure."

Hemp has been found in Germanic burials dating back to 500 BCE (Schultes 1973). This raises the possibility that Saxon folk custom, rather than herbal lore inherited from the texts of Galen and Dioscorides, established its use in England, although subsequent monastic praxis embraced both. *C. sativa* was cultivated in England during the Anglo-Saxon period (5th-11th centuries CE) to make rope, but it was also noted that "manured" hemp, used for coughs and jaundice, differed in its properties from "bastard" (wild-growing) hemp, the

latter being medicinal "against nodes and wennes and other hard tumours" (Schultes and Hoffmann 1992, p. 97). The *Herbarium* (11th century, rpt. 1984, CXVI, p.148) recommends "haenep" (glossed in Latin as *Cannabis sativa*) specifically for sore breasts: "gecnucude mid rysle, lege to pam breostan, heo toferep paet geswel; gyf paer hwylc gegaderung bip heo pa afeormap." (I translate this as "Rub [the herb] with fat, lay it to the breast, it will disperse the swelling; if there is a gathering of diseased matter it will purge it.")

Hemp enjoyed an enhanced respect under the Tudor monarchs, as with the onset of imperial longings, the navy's demand for rope increased. It was vigorously cultivated in England, and even planted at Jamestown, Virginia, in 1611 (Grinspoon and Bakalar 1997). Male and female plants were distinguished by the terms "carl" and "fimble" hemp, respectively, and the characteristics of summer and winter hemp assiduously noted. Parkinson's *Theatrum Botanicum* (1640) includes notes on its cultivation. The "drowning" of the carl hemp was an important part of its processing in preparation for use as fibre, and required skill, for too prolonged an immersion would cause the hemp to rot. It is interesting to note that the 19th-century reprint of Thomas Tusser's *Five Hundred Points of Good Husbandrie* (1812, originally published in 1557) contains an editorial comment to the effect that the neglect of the valuable hemp plant is one of the misfortunes arising from a dependence on foreign trade. The categorisation of non-psychoactive cannabis as an indigenous or naturalised British plant, serving as a useful source of fibre, clearly remained untroubled for centuries.

But this is only one aspect of the history of cannabis use in what is now termed "early modern" England. The English Renaissance herbals clearly indicate that, as for the Anglo-Saxons, hemp was a source of therapeutic constituents as well. It is clear that the Tudor herbalists, who by 1588 depended on extra-European sources for only 15% of their drugs (Bellamy 1992), were qualified by familiarity, as well as by their assimilation of Classical sources, to assess the virtues of cannabis as a medicinal herb.

"Water of hempe" was recommended in *The Vertuous Boke of Distillacioun* for headache and "for all hete wheresoe'er it be" (trans. Andrewes 1527). John Parkinson, in *Theatrum Botanicum* (1640), and Nicholas Culpeper (1652) subsequently confirmed this indication for the aromatic water. Richard Banckes (1525, p. 21) also demonstrates an awareness of the anti-pyretic property of cannabis: "its virtue is, if a man have the fever, fret well his pulse therwith, and he shall be whole."

William Turner (1551) offers his readers Latin, English, French and Dutch names for medicinal hemp, indicating widespread use in northern Europe. He follows the Classical authors in recommending it for earache and warning that it may impede fertility, and compares Dioscorides' discussion of hemp with

that of Pliny, emphasising that it (p. 112) "maketh soft the joints that are shrunk together."

Turner also echoes Simeon Sethy (p. 112): the seed "if taken out of measure, taketh men's wits from them, as coriander doth." This does not sound like personal testimony, yet it is clear that if the English Renaissance herbalists were sufficiently in thrall to the Classical lore-masters to preserve and repeat their conclusions, they were also capable of discussing those findings and comparing them with contemporary knowledge based on the authority of experience.

What is remarkable about Turner, for instance, is his critical use of eclectic sources: he is punctilious in his attempt to differentiate between what he has read and what he has understood through his own perceptions. In the Dodoens *Herbal* translated into English by Henry Lyte (1619), Lyte warns against the ingestion of the raw seeds in what may be the voice of experience, despite being based on Galen: the seeds are "contrarie to the stomach . . . and engendreth grosse and naughtie humors in all the bodie" (Schultes and Hoffmann 1992, p. 95). The mode of hemp preparation utilising dairy products such as butter (e.g., Culpeper 1652) is not copied from Classical sources but is a specifically Northern European practice. I conclude therefore that if Dioscorides, Galen et al. provided the literary basis of Tudor and Stuart writing about cannabis, their work was supplemented by a contemporary empirical awareness.

However, cannabis does not seem to have been recorded in English Renaissance herbals as an inebriant, any more than it was documented as such by the Anglo-Saxons. This is all the more curious since Prosper Alpinus (1591) had reported on its use as an intoxicant in Egypt, and given the extraordinary cosmopolitanism of the English at that time, and the fervour with which strange plants were investigated by the early Elizabethans, it is implausible to suppose that *hashish* was altogether unknown. Burton's resplendent *Anatomy of Melancholy* (1621) perhaps offers a clue to this puzzle: speaking of herbs which take away grief, he mentions "another called Bang, like in effect to Opium, which puts [men] for a time into a kind of Extasis, and makes them gently to laugh" (p. 593). It is clear from the context and word choice that Burton is repeating here information gleaned from a Hispanic text: significantly, he shows no awareness that the aromatic, resinous *bhang* is in any way related to the familiar English hemp.

The generation of herbalists who followed the Renaissance practitioners in England also approached cannabis with confidence and curiosity, discovering new applications or attempting to ascertain its mechanism of action. Culpeper listed *Cannabis sativa* in his famous *Herbal* (1652). With a wry aside on the disciplinary use of hempen rope (it is "good for something else than to make halters only" (p. 183), he applauded the healing virtues of the plant, e.g., "The emulsion of the seed is good for the jaundice, if there be ague accompanying it,

for it opens obstructions of the gall, and causes digestion of choler." He recommended cannabis for fluxes, colic and rheumatic pain, adding that the fresh root, "mixed with a little oil and butter, is good for burns," and the seed, seethed in milk till it releases its oils, for hot and dry coughs (Culpeper 1994, p. 183). The use of cannabis as a drying, warming plant that "openeth the passage of the gall" is anticipated in Gerard (1633, p. 709).

Culpeper was not the first to note the significance of the hempen knot. William Bullein had earlier (1562) claimed a socio-therapeutic action for cannabis, wittily asserting that "neckwede" is specific against necrosis of the body politic. Under the heading "Many good medicines made of hepe" [sic], he notes: "if there by any yonkers troubled with idelnesse and loytryng, hauyng neither learnying, nor willyng handes to labour, or that haue studied Phisicke so longe that he can giue his Masters purse a Purgacioun, and Countinghouse, a strong vomit . . . if there be any swashbuckler, common theef, ruffen or murtherer paste grace, the next remedie is this lace or corde . . . this is a purger, not of Melancholy, but a finall banisher of al them that be not fitt to liue In a common wealth" (Fol. xxviii).

Bullein's *Booke of Simples* (Fol. xxviii-ix of the *Bulwarke of Defence*) contains an exuberant listing of all the trades cannabis can serve: "without Hempe, sayle clothes, shroudes, staies, tacles, yarde lines, warps & cables can not be made, no Plowe or Carte can be without ropes, halters, trace etc. The Fisher and Fouler muste haue Hempe, to make their nettes. And no Archer can wante [i.e., be without] his bowe string: and the Malt man for his sackes. With it the bell is rong, to seruice in the church . . . "

He adds that cannabis is hot and dry, medicinally useful, *inter alia*, for conditions of cold contraction (applied as a hot poultice, the leaves and seeds "doe help against the contrarion, or shrinking of the sinewes"), and, stamped together with *Artemisia absinthum*, "to asswage swelling."

Hempseed assumes a more sinister aspect when it appears in a narcotic mixture of herbs to be steeped in wine, strained through a cloth woven by a whore, and taken as part of a 17th century ritual for questioning the dead (Deacon 1968). Further work needs to be done on herbal formulae for magical purposes, in order to determine whether the chemical components of the various plants created a desirable synergistic effect. It may be, for example, cannabis in some way modifies the effect of *Hyoscyamus niger*.

However that may be, it is certain that by 1700, cannabis had been a stalwart of English medicine for approximately a thousand years. An unproblematic component of our *Materia medica*, it continued to be used throughout the eighteenth and nineteenth centuries. Salmon (1710, p. 510) described indications for "the emulsion of the seed" primarily in terms of its usefulness in various forms of haemorrhage and intestinal flux. He recommends a cataplasm of the root of manured (i.e., cultivated) hemp, mixed with "Barley Flower" for sciat-

ica and pains in the hip joint. A Sheffield doctor (Short 1751) eulogised cannabis as specific for chronic uterine obstruction ("not only Months, but some Yeares"), and reports a case in which "when it could not break the Uterine or Vaginal vessels, the Woman threw up blood from the Lungs, but had [her period] naturally the next Time" (p. 138). A uterine action for cannabis was known to the Egyptians. The Ebers Papyrus, dating to 1550 BCE, notes that hemp mingled with honey, administered intra-vaginally, cools and contracts the uterus (Manniche 1989).

Cannabis formed part of the anti-diuretic formula in the *Medicine Britannica* (Short 1751), and he also used it for insect bites, wounds, ulcers, coughs and burns (p. 138): "An Emulsion of the Seed takes out fresh Marks of the Small Pox . . . It kills Worms in the Bowels or Ears of Man or Beast." Again, we see this English combination of the Classical herbal tradition with practical instruction: "the seed boiled in Milk till it burst, then strained, and five or six Ounces of it given several times to drink, has cured the Jaundice in many."

Ethan Russo (personal communication) has made a study of equivalent European sources including Marcandier's *Traité du Chanvre*, translated into English as *A Treatise on Hemp* (1764), which though expansive in echoing its classical and renaissance medical indications, failed to demonstrate an awareness of the inebriating properties of cannabis. Once more, the English seem not to have associated their familiar domestic herb with the intoxicant enjoyed in Egypt and the East.

Like all plant medicines, cannabis was less prominent following the Enlightenment, until O'Shaughnessy's work in 1839 revived its popularity. Cannabis regained its status as a popular medicine in England, but this time, the condensed aromatic cannabinoids found in the blocks of imported Indian resin enabled a new emphasis to be placed on its analgesic function. Even the eminently respectable Queen Victoria used hemp sent from her new dominion for menstrual cramps (BMA 1997), and Victorian doctors treated patients for a range of illnesses, including epilepsy and nervous disorders, with extracts of *Cannabis indica*.

How did a plant which early 20th century orthodox medicine enthusiastically summarised as an antipyretic, analgesic, anti-diuretic, anti-asthmatic, hypnotic, anti-anorectic, anti-emetic, and anticonvulsive muscle relaxant (BMA 1997; Grinspoon 1997) come, fifty years later, to be classified as being "of no therapeutic benefit," unavailable for use, inaccessible to research, categorized as Schedule 1 of the Misuse of Drugs Act, 1971?

That question must be answered with reference to the attempts of American and European governments to control domestic consumer behaviour, and influence the economies of other countries, by enacting laws that distinguish acceptable drugs from those deemed pernicious. The picaresque history of

cannabis legislation, recently the subject of much scholarly scrutiny, cannot be outlined here, but the historical weight of traditional usage must surely be re-evaluated in the near future, and cannabis once again be restored to recognition as a herb proper to English bodies.

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Introduction: Women and Cannabis: Medicine, Science, and Sociology

The *Journal of Cannabis Therapeutics: Studies in Endogenous, Herbal & Synthetic Cannabinoids* is pleased to present its second special issue on the subject of *Women and Cannabis: Medicine, Science, and Sociology.* This topic is particularly appropriate on a couple of levels. Firstly, medical research has been remiss in addressing women's issues on a historical basis. Secondly, many gender-specific conditions, and female-predominant medical conditions are popularly treated with cannabis (Grinspoon and Bakalar 1997). These include dysmenorrhea, migraine (Russo 2001; Russo 1998), fibromyalgia, and a wide variety of autoimmune disorders such as rheumatoid arthritis (Malfait et al. 2000), and multiple sclerosis. The latter receives particular attention in this publication.

This survey begins with a historical review of cannabis in treatment of obstetrical and gynecological conditions. A surprising volume and depth of documentation is evident, which only now is subject to scientific investigation and verification. A "fertile field" for additional research is evident.

An Italian research team, Bari et al., examine the critical role that endocannabinoids play in fertilization mechanisms. The last decade has revealed numerous physiological roles in which this system plays a key part.

Ester Fride follows with another illustration, that of endocannabinoids and neonatal feeding. It would seem that without this necessary endocannabinoid stimulus, we might all starve to death just as life was commencing. The presence of trace concentrations of endocannabinoids in breast milk underline the importance of this system in physiological maintenance of life and homeostasis.

In order to achieve successful birth, pregnancy maintenance is a critical prerequisite. Wei-Ni Lin Curry examines the controversial treatment of

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hyperemesis gravidarum with cannabis in an "underground research study." Provocative questions and possibilities result.

What of the sequelae of maternal cannabis usage? Peter Fried reviews the large body of literature that has examined the progeny of such pregnancies and their possible effects on cognition in children.

How should we educate about clinical cannabis? Mary Lynn Mathre tells us from the perspective of an addiction treatment nurse specialist.

Melanie Dreher presents an anthropological and sociological study from Jamaica that supports the prospect that cannabis, itself labeled as a drug of abuse, might well serve to treat and prevent addiction to cocaine, an idea first proposed in the 19th century (Mattison 1891), but still causing notice in the 21st. In the lyrics to his 1981 song, "Champagne and Reefer," blues artist, Muddy Waters commented on the issue (Waters 1981):

> I'm gonna get high
> Gonna get high just as sure as you know my name.
> Y'know I'm gonna get so high this morning
> It's going to be a crying shame.
> Well you know I'm gonna stick with my reefer
> Ain't gonna be messin' round with no cocaine.

Mila Jansen, an inventor and businesswoman from Holland, and Robbie Terris present the rationale behind the clinical use of cannabis as hashish, and the modern methods she has developed for its production.

Kirsten Müller-Vahl et al. review the effects of cannabis in the movement disorder, Tourette syndrome, and present a detailed case study where it seemed to be beneficial.

Clare Hodges comments on her affliction with multiple sclerosis, a cruel disease whose victims have been at the forefront of clinical cannabis claims. She documents her experience and those of other patients.

Denis Petro follows with a seminal review of the topic and the evidence to date that supports a role for cannabis in MS treatment.

We hope that this collection will advance the topic of women's medicine and at least promote the consideration of cannabis and cannabinoid treatment of recalcitrant clinical conditions.

Ethan Russo, MD

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Cannabis Treatments in Obstetrics and Gynecology: A Historical Review

Ethan Russo

SUMMARY. Cannabis has an ancient tradition of usage as a medicine in obstetrics and gynecology. This study presents that history in the literature to the present era, compares it to current ethnobotanical, clinical and epidemiological reports, and examines it in light of modern developments in cannabinoid research.

The author believes that cannabis extracts may represent an efficacious and safe alternative for treatment of a wide range of conditions in women including dysmenorrhea, dysuria, hyperemesis gravidarum, and menopausal symptoms. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

Ethan Russo, MD, is Clinical Assistant Professor of Medicine, University of Washington, Adjunct Associate Professor of Pharmacy, University of Montana, and Clinical Child and Adult Neurologist, Montana Neurobehavioral Specialists, 900 North Orange Street, Missoula, MT 58902 USA (E-mail: erusso@blackfoot.net).

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KEYWORDS. Cannabis, cannabinoids, medical marijuana, THC, obstetrics, gynecology, dysmenorrhea, miscarriage, childbirth, fertility, history of medicine

INTRODUCTION

For much of history the herbal lore of women has been secret. As pointed out in John Riddle's book, *Eve's Herbs* (Riddle 1997), botanical agents for control of reproduction have been known for millennia, but have often been forgotten over time or lost utterly, as in the case of the Greek contraceptive, *sylphion*. The same is true for other agents instrumental in women's health, frequently due to religious constraints. One botanical agent that exemplifies this lost knowledge is cannabis. As will be discussed, its role as an herbal remedy in obstetric and gynecological conditions is ancient, but will surprise most by its breadth and prevalence. Cannabis appears in this role across many cultures, Old World and New, classical and modern, among young and old, in a sort of herbal vanishing act. This study will attempt to bring some of that history to light, and place it in a modern scientific context.

THE ANCIENT WORLD AND MEDIEVAL MIDDLE AND FAR EAST

The earliest references to cannabis in female medical conditions probably originate in Ancient Mesopotamia. In the 7th century BCE, the Assyrian King Ashurbanipal assembled a library of manuscripts of vast scale, including Sumerian and Akkadian medical stone tablets dating to 2000 BCE. Specifically according to Thompson, *azallû*, as hemp seeds were mixed with other agents in beer for an unspecified female ailment (Thompson 1924). *Azallû* was also employed for difficult childbirth, and staying the menses when mixed with saffron and mint in beer (Thompson 1949). Usage of cannabis rectally and by fumigation was described for other indications.

Cannabis has remained in the Egyptian pharmacopoeia since pharaonic times (Mannische 1989), administered orally, rectally, vaginally, on the skin, in the eyes, and by fumigation. The Ebers Papyrus has been dated to the reign of Amenhotep I, circa 1534 BCE, while some hints suggest an origin closer to the 1st Dynasty in 3000 BCE (Ghalioungui 1987). One passage (Ebers Papyrus 821) describes use of cannabis as an aid to childbirth (p. 209): "Another: *smsm-t* [shemshemet]; ground in honey; introduced into her vagina (*iwf*). This is a contraction."

The *Zend-Avesta*, the holy book of Zoroastrianism, survives only in fragments dating from around 600 BCE in Persia. Some passages clearly point to psychoac-

tive effects of *Banga,* which is identified as hempseed by the translator (Darmesteter 1895). Its possible role as an abortifacient is noted as follows (Fargard XV, IIb., 14 (43), p. 179):

> And the damsel goes to the old woman and applies to her for one of her drugs, that she may procure her miscarriage; and the old woman brings her some Banga, or Shaêta ["another sort of narcotic"], a drug that kills in womb or one that expels out of the womb, or some other of the drugs that produce miscarriage . . .

Physical evidence to support the presence of medicinal cannabis use in Israel/Palestine was found by Zias et al. (1993) in a burial tomb, where the skeleton of a 14 year-old girl was found along with 4th century bronze coins. She apparently had failed to deliver a term fetus due to cephalopelvic disproportion. Gray carbonized material was noted in the abdominal area (Figure 1). Analysis revealed phytocannabinoid metabolites. The authors stated (p. 363), "We assume

FIGURE 1. Carbonized residue from 4th century Judea, containing phytocannabinoid elements, as a presumed obstetrical aid. (Permission Courtesy of the Israel Antiquities Authority.)

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that the ashes found in the tomb were cannabis, burned in a vessel and administered to the young girl as an inhalant to facilitate the birth process."

Budge (1913) noted Syriac use of cannabis to treat anal fissures, as might occur postpartum.

Dwarakanath (1965) described a series of Ayurvedic and Arabic tradition preparations containing cannabis indicated as aphrodisiacs and treatments for pain. It was noted that cannabis was employed in Indian folk medicine onwards from the 4th-3rd centuries BCE.

In the 9th century, Sabur ibn Sahl in Persia cited use of cannabis in the *Al-Aqrabadhin Al-Saghir*, the first *materia medica* in Arabic (Kahl 1994). According to the translation of Indalecio Lozano of the Universidad de Granada, Spain (personal communication, Feb. 4, 2002), an intranasal base preparation of juice from cannabis seeds was mixed with a variety of other herbs to treat migraine, calm uterine pains, prevent miscarriage, and preserve fetuses in their mothers' abdomens.

In the 11th century, the Andalusian physician, Ibn Wafid al-Lajmi indicated that drying qualities of hemp seeds would inhibit maternal milk production. Tabit ibn Qurra claimed that they would reduce female genital lubrication when mixed in a potion with lentils and vinegar (Lozano 1993).

In the 13th century, the famous Persian physician, Avicenna (ibn Sina) recommended seeds and leaves of cannabis to resolve and expel uterine gases (Lozano 1998).

According to Lozano (2001), Ibn al-Baytar prescribed hemp seed oil for treatment of hardening and contraction of the uterus (al-Baytar 1291).

In the *Makhzan-ul-Adwiya,* a 17th century Persian medical text, it was claimed that cannabis leaf juice (Dymock 1884, p. 606) "checks the discharge in diarrhoea and gonorrhoea, and is diuretic."

Farid Alakbarov has recently brought to light the amazing richness of cannabis therapeutics of medieval Azerbaijan (Alakbarov 2001). Four citations are pertinent. Muhammad Riza Shirwani employed hempseed oil in the 17th century to treat uterine tumors. Contemporaneously, another author advised likewise (Mu'min 1669). Tibbnama recommended a poultice of cannabis stems and leaves to treat hemorrhoids, and the leaves mixed with asafetida for "hysteria" (Tibbnama 1712).

In China, the *Pen T'sao Kang Mu*, or *Bencao Gang Mu* was compiled by Li Shih-Chen in 1596 based on ancient traditions. This was later translated as Chinese *Materia Medica* (Stuart 1928). In it, cannabis flowers were recommended for menstrual disorders. Seed kernels were employed for postpartum difficulties. It was also observed (p. 91), "The juice of the root is . . . thought to have a beneficial action in retained placenta and post-partum hemorrhage."

EUROPEAN AND WESTERN MEDICINE

The earliest European references to the use of cannabis in women's medicine may derive from Anglo-Saxon sources. In the 11th century *Old English Herbarium* (Vriend 1984, CXVI, p.148), *haenep*, or hemp is recommended for sore breasts. This was translated as follows (Crawford 2002, p. 74): "Rub [the herb] with fat, lay it to the breast, it will disperse the swelling; if there is a gathering of diseased matter it will purge it."

The Österreichische Nationalbibliothek in Vienna, Austria displays a manuscript of the *Codex Vindobonensis 93*, said to be a 13th century southern Italian copy of a work produced in previous centuries, or even earlier Roman sources (Zotter 1996). Plate 108 depicts a clearly recognizable cannabis plant above the figure of a bare-breasted woman (Figure 2). According to a translation of Drs. David Deakle and Daniel Westberg (personal communication 2002), the Latin inscription describes the use of cannabis mixed into an ointment and rubbed on the breasts to reduce swelling and pain.

A translation in Old Catalan of Ibn Wafid's work above, interpreted it differently, indicating that hemp seeds, when eaten in great quantity, liberate maternal milk and treat pain of amenorrhea (Lozano 1993; personal communication, 2002).

Citing the *Kräuterbuch* of Tabernaemontanus in 1564, it was noted (Kabelik, Krejei, and Santavy 1960, p. 7), "Women stooping due to a disease of the uterus were said to stand up straight again after having inhaled the smoke of burning cannabis."

In England, in the *Theatrum Botanicum (Parkinson, Bonham, and L'Obel 1640)*, John Parkinson noted (p. 598) "Hempe is cold and dry . . . the Emulsion or decoction of the seede, stayeth laskes and fluxes that are continuall, . . ."

In 1696, Georg Eberhard Rumpf (Rumphius), a German physician in the service of the Dutch crown, reported on the use of cannabis root in Indonesia to treat gonorrhea (Rumpf and Beekman 1981, p. 197): "the green leaves of the female plant, cooked in water with Nutmeg, to drink to folks who felt a great oppression in their breasts, along with stabs, as if they had Pleuritis too."

According to Hamilton (1852), Valentini recommended hemp seed emulsion in the previous century to treat *furor uterinus*, a loosely defined malady of the era, frequently associated with nymphomania, melancholia or other ills, more fully discussed by Dixon (1994).

In his book, *Medicina Britannica*, Short (1751) employed cannabis for treatment of obstruction of the menses, even of chronic duration. In one case, he stated (p. 137-138), "I once ordered only the Hemp alone, where they [menses] had been obstructed not only Months, but some Years, with Success; and, when it could not break the Uterine or Vaginal Vessels, the Woman threw up Blood from the Lungs, but had them naturally the next Time."

FIGURE 2. Plate from the *Codex Vindobonensis 93* from the 13th century or earlier, depicting use of cannabis to allay breast swelling and pain. (From Bildarchiv d., with permission of the Österreichishe Nationalbibliothek, Vienna, Austria.)

Short (1751) also described a combination of hemp in "New-wort" (steeped crushed grain used in brewing beer) with feverfew (*Tanacetum parthenium*) and pennyroyal (*Mentha pulegium*) employed on three successive nights to (p. 137) "bring down the *Menses minime fallax*." Feverfew has anti-inflammatory effects, while pennyroyal is a known abortifacient (Riddle 1997). Thus, this treatment may well have induced miscarriage.

Finally, Short (1751, p. 138) noted this of a complex herbal mixture with hemp: "Some pretend the following a great Secret against Pissing the Bed . . ."

In 1794, the *Edinburgh New Dispensatory* noted use of a hemp seed oil emulsion in milk, useful for "heat of urine," "incontinence of urine," and "restraining venereal appetites" (Lewis 1794, p. 126).

After the reintroduction of cannabis to Western medicine in the form of solid oral extracts and tinctures by O'Shaughnessy (1842), its spectrum of activity quickly extended to many conditions. The first citation of its use for uterine hemorrhage in modern medicine is probably from Churchill (1849), and its discovery for this indication was apparently serendipitous (p. 512):

> We possess two remedies for these excessive discharges, at the time of the menses going off, which were not in use in Dr. Fothergill's time [18th century]. I mean *ergot of rye*, and *tincture of Indian hemp*. . . .
>
> The property of Indian hemp, of restraining uterine hemorrhage, has only been known to the profession a year or two. It was accidentally discovered by my friend, Dr Maguire of Castleknock, and since then it has been extensively tried by different medical men in Dublin, and by myself, with considerable success. The tincture of the resin is the most efficacious preparation, and it may be given in doses of from five to fifteen or twenty drops three times a day, in water. Its effects, in many cases, are very marked, often instantaneous, but generally complete after three or four doses. In some few cases of ulceration in which I have tried it on account of the hemorrhage, it seemed to be equally beneficial.

Alexander Christison extended the work of Churchill and applied Indian hemp to the problem of childbirth (Christison 1851), offering the following (pp. 117-118):

> Indian hemp appears to possess a remarkable power of increasing the force of uterine contraction during labour . . .
>
> One woman, in her first confinement, had forty minims of the tincture of cannabis one hour before the birth of the child. The os uteri was then of the size of a shilling, the parts very tender, with induration around the os uteri. The pains quickly became very strong, so much so as to burst the membranes, and project the liquor amnii to some distance, and soon the head

> was born. The uterus subsequently contracted well.
>
> Another, in her first confinement, had one drachm of the tincture, when the os uteri was rigid, and the size of a half-crown ; from this the labour became very rapid.
>
> Another, in her first confinement, had also one drachm of the tincture, when the os uteri was the size of a half-crown. Labour advanced very rapidly, and the child was born in an hour and a-half. There were severe after-pains.

Subsequently, Christison studied the oxytocic effects of cannabis tincture systematically in seven cases. He made several conclusions (pp. 120-121):

> Shortening of the [pain] interval was in general a more conspicuous phenomenon than prolongation of the pain.–
>
> It is worthy of remark, that in none of these cases were the ordinary physiological effects produced ; there was no excitement or intoxicating action, and there did not seem to be the least tendency to sleep in any of them.
>
> . . . While the effect of ergot does not come on for some considerable time, that of hemp, if it is to appear, is observed within two or three minutes. Secondly,-The action of ergot is of a lasting character, that of hemp is confined to a few pain shortly after its administration. Thirdly,-The action of hemp is more energetic, and perhaps more certainly induced, than that of ergot.
>
> There appears little doubt, then, that the Indian hemp may often prove of essential service in promoting uterine contraction in tedious labours.

Grigor (1852) also examined the role of tincture of *Cannabis indica* in facilitation of childbirth. In 9 cases, little was noticeable, but in 7, including 5 primiparous women (p. 125):

> I have noticed the contractions acquire great increase of strength and frequency immediately on swallowing the drug, and have seen four or five minutes ere the effect ensued ; . . . when effectual it is capable of bringing the labour to a happy conclusion considerably within a half of the time that would other have been required . . .
>
> I have not observed it to possess any anaesthetic effects . . .
>
> I consider the expulsive action of the cannabis to be stronger than that of ergot, but less certain in its effect . . .
>
> . . . nor have unpleasant consequences, so far as I have seen, appeared afterwards.

By 1854, the first uses of therapeutic cannabis were acknowledged in the *Dispensatory of the United States* (Wood and Bache 1854), and these effects of cannabis to hasten childbirth without anesthesia were noted (p. 339).

Willis (1859) reviewed past literature on therapeutic cannabis, and then described his own experience, which was frequently cited subsequently (p. 176):

> I have used the Indian hemp for some time and in many diseases, especially in those connected with the womb, in neuralgic dysmenorrhoea, in menorrhagia, in cessation of menstruation where the red discharge alternates with uterine leucorrhoea of long continuance, in repeated attacks of uterine hemorrhage, in all cases of nervous excitability, and in tedious labor, where there is restlessness of the patient, with ineffectual propulsive action of the uterus.
>
> . . . I was led to the use of hemp in puerperal convulsions, having also seen its beneficial effects in convulsions in general, after all the common remedies had been tried without relief.

Willis opined that based on literature and experience (p. 178), "It is a safe conclusion, from the many facts which have been published, that Indian hemp deserves further trial; in all cases making sure that the preparation used is good."

McMeens (1860) headed an Ohio State Commission that examined medical effects of cannabis. In addition to many references cited above, he reported on a Dr. M.D. Mooney of Georgia, who noted that a mixture of milk sugar and *Cannabis indica* extract (20 mg) taken every 3-4 h to treat gonorrhea was (p. 90) "successful in every case in from five to seven days."

That same year, a popular text (Stillé 1860) cited many contemporary authorities, noted irregular effects, and opined (vol. 2, p. 88), "From some experiments, cannabis would appear to excite contractions of the uterus."

Wright (1862) specifically noted the benefit of cannabis in relieving vomiting of pregnancy. In an initial letter, he discussed the case of a woman where all other available remedies had failed (pp. 246-247): "In a patient of mine, who was suffering to an extent that threatened death, with vomiting, I found the vomiting completely arrested by cannabis indica, given in repeated doses of three grains every four hours, until several doses were taken." He later revisited the issue in a subsequent article (Wright 1863), and explained (p. 75), "*Cannabis indica* does not paralyze the nerves, but strengthens them directly. It does not *constipate* by paralysis–it *cures* by beneficent virtues."

Silver (1870) devoted an entire article to the use of cannabis to treat menorrhagia and dysmenorrhea, reporting 5 cases in detail, all relieved nicely with cannabis within a few doses. He also referred to a colleague, who had never failed in over a hundred cases to control pain and discomfort in these disorders within 3 doses. When flow was not checked after early treatment, Silver felt this

diagnostic of "organic mischief" (p. 60) due to uterine fibroids, cervical carcinoma or other cause.

Grailey Hewitt authored a comprehensive textbook of obstetrics and gynecology. Cannabis was endorsed as a hemostatic treatment for menorrhagia, analgesic in dysmenorrhea and uterine cancer (Hewitt 1872). He compared it to other available remedies for the latter, including belladonna, hyoscyamus, opium and chloroform, remarking (p. 416), "The Indian hemp is, however, better entitled to consideration, and in many cases undoubtedly exercises a marked influence in allaying or preventing pain."

In another contemporary text (Scudder 1875), the author observed (p. 100), "I have employed the Cannabis specially to relieve irritation of the kidneys, bladder and urethra. It will be found especially beneficial in vesical and urethral irritation, and is an excellent remedy in the treatment of gonorrhoea."

Cannabis was also popular in France for Ob-Gyn indications. Racime (1876) described medical usage of hashish and Indian hemp (p. 443, [translation EBR]): "In women, hemp has a most manifest action on the uterus; this action translates itself into a contraction of the uterine muscular fibers."

A selection from a broad French review follows (Michel 1880, pp. 111-112 [translation EBR]):

> Illnesses of the genito-urinary organs.-Indian hemp has been employed in a large number of uterine affections, but principally in the diverse disturbances of menstruation. The tendency of authors is to administer it while the pain element predominates. . . .
>
> We have ourselves administered it often and in diverse cases of uterine hemorrhage: we have always seen success as well in postpartum hemorrhages, cases in which we employ it today in preference to the ergot of rye . . .
>
> . . . The reader would well permit us to affirm that but one first spoonful of the potion against menorrhagia (see the formula) has almost always succeeded in sufficiently diminishing the flow of blood. Rarely, the patient has had to take 4 spoonfuls. What has certainly struck us in its proper action is that its influence seems to have an effect on the following cycles; the Indian hemp acts, according to our observation and the remarks of Churchill himself, like a regulator of the catamenial function. Administered, in effect, during one sole period, sometimes two, rarely three, the menses return henceforth to just proportions and all medication becomes unnecessary. I know not of a similar effect that has been reported with ergotine or ergot of rye.

Michel also endorsed cannabis treatment for blennorrhagia, or bloody uterine mucous discharge.

In 1883, two consecutive letters to the *British Medical Journal* attested to the benefits of extract of *Cannabis indica* in menorrhagia, treating both pain and bleeding successfully with a few doses. In the first, cannabis was termed "a valuable remedy" (Brown 1883, p. 1002):

> Indian hemp has such specific use in menorrhagia–there is no medicine which has given such good results . . . A few doses {commencing with 5 minims of tincture} are sufficient . . . The failures are so few, that I venture to call it a specific in menorrhagia. The drug deserves a trial.

The second letter also extolled the benefits of cannabis (Batho 1883, p. 1002):

> . . . considerable experience of its employment in menorrhagia, more especially in India, has convinced me that it is, in that country at all events, one of the most reliable means at our disposal. I feel inclined to go further, and state that it is par excellence the remedy for that condition, which, unfortunately, is very frequent in India.
>
> I have ordered it, not once, but repeatedly, in such cases and always with satisfactory results. The form used has been the tincture, and the dose ten to twenty minims, repeated once or twice in the twenty-four hours. It is so certain in its power of controlling menorrhagia, that it is a valuable aid to diagnosis in cases where it is uncertain whether an early abortion may or may not have occurred. Over the hemorrhage attending the latter condition, it appears to exercise but little force. I can recall one case in my practice in India, where my patient had lost profusely at each period for years, until the tincture was ordered; subsequently, by commencing its use, as a matter of routine, at the commencement of each flow, the amount was reduced to the ordinary limits, with corresponding benefit to the general health. Neither I this, nor in any other instance in which I prescribed the drug, were any disagreeable physiological effects observed.

One dissenting voice of the era was that of Oliver (1883) who felt that cannabis was not useful in dysmenorrhea since (p. 905) "its action seems so variable and the preparation itself so unreliable, as to be hardly worthy of a place on our list of remedial agents at all." Quality control problems with cannabis were a frequent concern throughout its reign in Western medicine.

Sydney Ringer, the British pioneer of intravenous fluid therapy, observed the following of *Cannabis indica* extract (Ringer 1886, p. 563):

> It is said to relieve dysuria, and strangury, and to be useful in retention of urine, dependent on paralysis from spinal disease. It is used occasionally in gonorrhoea. It is very useful in menorrhagia, or dysmenorrhoea. Half a grain to a grain thrice daily, though a grain every two hours, or hourly, is

> sometime required in those who can tolerate so large a dose, often relieve the pain of dysmenorrhoea. It is said to increase the energy of the internal contractions.

In India, it was reported of *Cannabis indica* (McConnell 1888, p. 95), "its powerful effect in controlling uterine hemorrhage (menorrhagia, &c.) has been repeatedly recorded by competent observers, and its employment for the relief of such affections is well understood and more or less extensively resorted to."

Farlow (1889) penned a treatise on the use of rectal preparations of cannabis describing its use in young women before marriage to alleviate premenstrual symptoms and subsequent dysmenorrhea (p. 508):

> If the excitement can be moderated, if the pelvic organs can be made less irritable, there will be less pain, less hemorrhage, less weakness, and consequently a much longer period of health between the catamenia. This, I feel sure, can often be very successfully done by the rectal use of belladonna and cannabis indica, beginning a few days before the menstrual symptoms or prodromes appear.

Farlow continued by describing another setting in sexually active, but nulliparous women (p. 508):

> After marriage and before childbirth, the uterus and pelvis, especially the left ovary, are very liable to be tender and irritable, even when there is no evident organic disease. The backache, bearing down, pain in the side, groin and legs, the frequent micturition, painful coitus, constipation and headache are often much relieved by the suppositories.

Finally, Farlow mentioned another cannabis indication (p. 580): "At the menopause the well-known symptoms, the various reflexes, the excitement, the irritability, and pain in the neck of the bladder, flashes of heat, and cold, according to my experience, can frequently be much mitigated, by the suppositories."

Farlow employed low doses of these agents, 1/4 grain each (15 mg) or extracts of belladonna and *Cannabis indica*, administered by rectal suppository at night, or bid. Apparently no intoxication was necessary for therapeutic benefit (p. 509): "I do not think there is anything to be gained by pushing the drugs to their physiological action."

Aulde (1890) recommended cannabis extract for dysmenorrhea, sometimes combined with gelsemium (pp. 525-526):

> The majority of these cases uncomplicated by displacements, such as seen in young girls and married women, will be promptly benefited, and the menstrual flow appears, when there is no further trouble until the next pe-

riod.

> . . . Cannabis has been highly recommended for the relief of *menorrhagia*, but is not curative in the true sense of the term.

Sir John Russell Reynolds was personal physician to Queen Victoria, and it has been widely acknowledged that she received monthly doses of *Cannabis indica* for menstrual discomfort throughout her adult life. In 1890, after more than thirty years' experience with the agent, Reynolds reported (Reynolds 1890, p. 38), "Indian hemp . . . is of great service in cases of simple spasmodic dysmenorrhoea."

Another textbook of the era noted the following therapeutic indications for *Cannabis indica* (Cowperthwaite 1891, p. 188): "Said to be especially useful in gonorrhoea when the chordee is well marked. Uterine colic."

J.B. Mattison wrote extensively on therapeutic cannabis. He noted the following among several gynecological conditions reviewed (Mattison 1891, p. 268): "In genito-urinary disorders it often acts kindly-the renal pain of Bright's disease ; and it calms the pain of clap equal to sandal or copaiva, and is less unpleasant."

The Indian Hemp Drugs Commission of 1893-1894 exhaustively examined the uses and abuses of cannabis, noting its indication for prolonged labor and dysmenorrhea (Kaplan 1969; Commission 1894).

In this era, patent medicines containing cannabis were very common. One preparation, named "Dysmenine," contained cannabis with a variety of other herbal tinctures, "Indicated for Dysmenorrhea, Menstrual Colic, and Cramps" (Figure 3). Interestingly, one component was capsicum, raising the possibility of synergistic action on cannabinoid and vanilloid receptors.

An 1898 text opined of the fluidextract of cannabis (Lilly 1898, p. 32), "Its anodyne power is marked in chronic metritis and dysmenorrhea."

Shoemaker (1899) reported a case of endometritis with metrorrhagia, that required surgery, but in which (p. 481) "Marked relief of symptom was afforded, however, by the administration of Indian hemp. It relieved pain and diminished hemorrhage, and was highly valued by the patient."

Lewis (1900) observed the following (p. 251):

> Dysmenorrhea, not due to anatomical of inflammatory causes, is, in my opinion, one of the principal indications for indian hemp. No other drug acts so promptly and with fewer after effects.
>
> From my own personal observation, I am convinced that cannabis indica does exert a powerful influence on muscular contraction, particularly of the uterus. It may not, as Bartholow says, have the power of initiating uterine contraction, but I have demonstrated time and time again to my own satisfaction that the presence of the merest contractile effort is enough to permit its fullest effects. It is therefore of some service in uterine hemor-

> rhage, but since its action is much slower than that of ergot, it is not as useful in those sudden hemorrhages great enough to require immediate check. I have noticed, however, that ergot is considerably quicker and more prolonged in its action when combined with cannabis indica.
>
> The drug is very useful in profuse menstruation, decreasing the flow nicely without completely arresting it, as ergot very frequently and improperly does.

Felter and Lloyd (1900) described numerous Ob-Gyn indications for cannabis (pp. 426-427):

> The pains of *chronic rheumatism, sciatica, spinal meningitis, dysmenorrhea, endometritis, subinvolution*, and the vague pains of *amenorrhoea*, with depression, call for cannabis. Owing to a special action upon the reproductive apparatus, it is accredited with averting *threatened abortion*. . . .
>
> Cannabis is said in many cases to increase the strength of the uterine contractions during parturition, in atonic conditions, without the unpleasant consequences of ergot, and for which purpose it should be used in the form of tincture (see below), 30 drops, or specific cannabis, 10 drops, in sweetened water or mucilage, as often as required. In *menorrhagia*, the tincture in doses of 5 or 10 drops, 3 or 4 times a day, has checked the discharge in 24 or 48 hours.
>
> The greatest reputation of cannabis has been acquired from its prompt results in certain disorders of the genito-urinary tract. In fact, its second great keynote or indication is irritation of the genito-urinary tract, and the indication is even of more value when associated with general nervous depression.
>
> It is therefore useful in *gonorrhoeas, chronic irritation of the bladder, in chronic cystitis*, with painful micturition, and in *painful urinary affections generally*. It makes no difference whether a urethritis be specific or not, or whether it is acute or chronic, the irritation is a sufficient guide to the selection of cannabis. Use it in *gonorrhoea* to relieve the *ardor urinae*, and to prevent urethral spasm and avert chordee, and in *gleet*, to relive the irritation and discharge; employ it also in *spasm of the vesical sphincter*, in *dysuria* and in *strangury*, when spasmodic. Burning and scalding in passing urine, with frequent desire to micturate, are always relieved by cannabis.

The authors clearly understood that the potency of the preparation directly affected clinical results. While both Indian hemp and American hemp were said to be effective, much higher doses of the latter were said to be required.

In a popular American text of the era, Bartholow (1903) noted (p. 557):

FIGURE 3. Photo of “Dysmenine” a late 19th century patent medicine for menstrual cramps, containing cannabis. (Photo by Ethan Russo, with permission of Michael Krawitz, the Cannabis Museum.)

> It is well established that hemp has the power to promote uterine contractions. It can not initiate them, but increased their energy when action has begun. It may be given with ergot. In consequence of this power which it possesses to affect the muscular tissue of organic life, hemp is used successfully in the treatment of *menorrhagia*. It is said to be especially useful in that form of *menorrhagia* which occurs in the climacteric period (Churchill). It has, more recently, been show to possess the power to arrest *hemorrhage* from any point, but it is chiefly in menorrhagia that much good is accomplished. . . .
>
> This agent has also been used with success in the treatment of *gonorrhoea*. It diminishes the local inflammation, allays chordee, and lessens the pain and irritation, with accompanying restlessness.

In Ceylon, Ratnam (1916) defended use of therapeutic cannabis against legislative challenges (p. 37): "I and other medical practitioners have used it extensively in the treatment of tetanus, asthma and uterine disorders, especially dysmenorrhea and menorrhagia."

In a text of the era, cannabis was deemed useful in menopausal headaches (Hare 1922), as well as the following (p. 182):

> In cases of *uterine subinvolution*, *chronic inflammation*, and *irritation* cannabis is of great value, and it has been found of service in *metrorrhagia* and *nervous and spasmodic dysmenorrhea*. Not only does it relieve pain, but it also seems to act favorably upon the muscular fibers of the uterus.

Another popular text (Sajous and Sajous 1924) cited cannabis as an analgesic for menopause, uterine disturbances, dysmenorrhea, menorrhagia and impending abortion, and postpartum hemorrhage.

In 1928, in *Pharmacotherapeutics, materia medica and drug action*, the authors remarked on the ability of cannabis to counteract "painful cramps" and its "particular influence over visceral pain" (Solis-Cohen and Githens 1928, p. 1702). More specifically, they noted (p. 1705):

> Cannabis acts favorably upon the uterine musculature and may be used as a synergist to ergot in sluggish labor. It is useful also in relieving the pain of chronic *metritis* and *dysmenorrhea* and reduces the flow in *menorrhagia*. It is employed as a symptomatic remedy in *gonorrhea* in doses of 1/4 grain (0.015 Gm.) of the extract four times a day, relieving the pain, dysuria, and chordee.

An anonymous editor (probably Morris Fishbein) noted the ability of cannabis to achieve a labor with pain burden substantially reduced or eliminated, followed by a tranquil sleep (Anonymous 1930, p. 1165):

> Hence a woman in labor may have a more or less painless labor. If a sufficient amount of the drug is taken, the patient may fall into a tranquil sleep form which she will awaken refreshed. . . . As far as is known, a baby born of a mother intoxicated with cannabis will not be abnormal in any way.

The *British Pharmaceutical Codex* retained an indication for cannabis in treatment of dysmenorrhea in 1934 (Pharmaceutical Society of Great Britain 1934).

Despite the fact that cannabis had been dropped from the *National Formulary* the previous year, Morris Fishbein, the editor of the *Journal of the American Medical Association*, continued to recommend cannabis in migraine associated with menstruation (Fishbein 1942, p. 326):

> In this instance the patient may be given either sodium bromide or fluidextract of cannabis three days before the onset of the menstrual period, continued daily until three days after the menstrual period. . . . The dose of fluidextract of cannabis is five drops three times daily, increased daily by one drop until eleven drops, three times daily, are taken. Then the dosage is reduced by one drop daily until 5 drops are taken three times daily and so on.

Medical investigation of cannabis persisted in Czechoslovakia. One group noted success in use of a cannabis extract in alcohol and glycerine to treat rhagades, or fissures, on the nipples of nursing women to prevent staphylococcal mastitis (Kabelik, Krejei, and Santavy 1960).

MODERN ETHNOBOTANY OF CANNABIS IN OBSTETRICS AND GYNECOLOGY

In the folk medicine of Germany, in the late 19th century (Rätsch 1998, p. 122), a cannabis preparation was "laid on the painful breasts of women who have given birth; hemp oil is also rubbed onto these areas; hempseed milk is used to treat bladder pains and dropsy."

Although the carminative properties of cannabis seeds had been noted since the time of Galen, Lozano (2001) notes that al-Mayusi (1877) claimed similar properties for the leaves, and to treat uterine gases.

In 19th century Persia, Schlimmer (1874) reported his observations on usage of *Cannabis indica* leaves as a treatment for urethritis associated with the practice of prostitution. In modern Iran, Zargari (1990) notes continued use of *Cannabis sativa* seed oil rubbed on the breasts to diminish or even completely prevent lactation.

Cannabis or *nasha* was employed medicinally despite Soviet prohibition in Tashkent in the 1930s (Benet 1975, pp. 46-47): "A mixture of lamb's fat with *nasha* is recommended for brides to use on their wedding night to reduce the pain of defloration." In the same culture (p. 47), "An ointment made by mixing hashish with tobacco is used by some women to shrink the vagina and prevent fluor alvus [leukorrhea]." More fancifully, Benet noted that in German folk medicine (p. 46), "sprigs of hemp were placed over the stomach and ankles to prevent convulsions and difficult childbirth."

Nadkarni (1976) reported the use in India of a poultice of cannabis for hemorrhoids, and (p. 263) "The concentrated resin exudate (resinous matters) extracted from the leaves and flowering tops or agglutinated spikes of C. sativa, and known as *nasha* or *charas* . . . is valuable in preventing and curing . . . dysuria and in relieving pain in dysmenorrhea and menorrhagia . . ."

In a book about medicinal plants of India (Dastur 1962), we see the following (p. 67): "Charas [hashish] . . . is of great value in-dysuria . . . it is also used as an anaesthetic in dysmenorrhea . . . . Charas is usually given in one-sixth to one-fourth grain doses." A seed infusion was also employed to treat gonorrhea.

Aldrich (1977) has extensively documented the Tantric use of cannabis in India from the 7th century onward as an aid to sexual pleasure and enlightenment (p. 229):

> The Kama Sutra and Ananga Ranga eloquently detail Hindu sexual techniques, and the Tantras transform such sexual practices into a means of meditational yoga.
>
> . . . In Hindu Tantrism, the female energy (shakti) is dynamic and paramount: the male is passive and takes all his vitality from the shakti. . . . In Buddhist Tantra it is just the opposite: the male is active and assumes the dynamic role of compassion, while the female is the passive embodiment of wisdom.

We have little modern research to document a biochemical basis to these claims, which persist, nonetheless. In his inimitable prose, Ott (2002, p. 29) has stated of cannabis, "many women I have known are effusively enthusiastic about its aphrodisiacal amatory tributes."

A treatise on cannabis usage in India includes the following citation (Chopra and Chopra 1957, p. 12): "It [cannabis resin] is considered a sovereign remedy for relieving pain in dysmenorrhea and menorrhagia, and against dysurea."

In Cambodia, mothers reportedly use hemp products extensively after birth (Martin 1975), making an infusion of ten flowering tops to a liter of water to provide a sense of well-being. When insufficient milk is present for nursing, female hemp flowers are combined with other herbs for ingestion. An alcoholic extract of cannabis and various barks is said to alleviate postpartum stiffness. Another hemp extract mixture is employed to cure hemorrhoids and polyps of the sex organs.

In Vietnam (Martin 1975), cannabis seed kernels in a preparation called sac thuoc are said to cure dysmenorrhea, or provide a feeling of wellness after childbirth. Citing Martin's work, Rubin noted the following usage in Vietnam (Rubin 1976, p. 3): "21 kernels boiled in water may be given to the expectant mother to reset the neonate in normal position at birth."

Hemp is of ancient use in China, but it was noted (Shou-zhong 1997, p. 148): "In modern clinical practice, Hemp Seeds are still in wide use. They are able to . . . promote lactation, hasten delivery, and disinhibit urination and defecation."

Perry and Metzger (1980) noted continued folk use of cannabis in China and Southeast Asia, where the seeds were specially prepared for treatment of uterine prolapse and as a birthing aid.

In South Africa, a Sotho herbalist used cannabis to facilitate childbirth (Hewat 1906, p. 98), and was "in the habit of getting his patient stupified by much smoking of dagga."

In modern times, urban Africans have also employed cannabis medicinally for a number of purposes (Du Toit 1980), as one informant related (p. 209):

> ". . . pregnant women should always have some burnt for her so as to have a completely healthy child." But is particularly during childbirth that "pregnant women were given dagga to make them brave," and "so that they wouldn't feel pain."

In Brazil, it was observed (Hutchinson 1975, p. 180), "Such an infusion [of marijuana leaves] is taken to relieve rheumatism, 'female troubles,' colic and other common complaints."

In a 20th century English herbal, Grieve (1971) noted the following uses of hemp (p. 397): "The tincture helps parturition, and is used in senile catarrh, gonorrhoea, menorrhagia, chronic cystitis and all painful urinary affections. An infusion of the seed is useful in after pains and prolapsus uteri." Dosages were provided (p. 397): "Of tincture for menorrhagia, 5 to 10 minims. Three to four times a day (i.e., 24 grains of resinous extract in a fluid ounce of rectified spirit)."

Finally, this passage was offered (p. 397): "The following is stated to be a certain cure for gonorrhoea. Take equal parts of tops of male and female hemp in blossom. Bruise in a mortar, express the juice, and add an equal portion of alcohol. Take 1 to 3 drops every two to three hours."

Merzouki et al. (Merzouki, Ed-derfoufi, and Molero Mesa 2000) have examined the usage of cannabis as part of herbal mixtures employed by Moroccan herbalists to induce therapeutic abortion, concluding that the cannabis component did not produce this effect, but rather other clearly toxic components were responsible. The herbal mixture is applied per vaginam, or alternatively, its smoke is fumigated in close proximity to the genitals (Merzouki 2001).

By the late 1960s, cannabis cures entered the scene in modern America. A popular treatise on marijuana noted medicinal effects (Margolis and Clorfene 1969, p. 26):

> You'll also discover that grass is an analgesic, and will reduce pain considerably. As a matter of fact, many women use it for dysmenorrhea or menorrhagia when they're out of Pamprin or Midol. So if you have an upset stomach, or suffer from pain of neuritis or neuralgia, smoke grass. If pains persist, smoke more grass.

Popular cannabis folklore, thus, did not escape American consciousness. Another example was noted by Thompson (1972, p. 3): "In the Jack's Creek area of Fayette County, Kentucky, poultices with hemp leaves are supposed to relieve hemorrhoidal pains and bleeding when applied in the appropriate area of the human body."

RECENT THEORY AND CLINICAL DATA

Solomon Snyder, the discoverer of opiate receptors, examined cannabis' pros and cons as an analgesic (Snyder 1971, p. 14):

> For there are many conditions, such as migraine headaches or menstrual cramps, where something as mild as aspirin gives insufficient relief and opiates are too powerful, not to mention their potential for addiction. Cannabis might conceivably fulfill a useful role in such conditions.

In the mid-1970s, Noyes et al. wrote several articles on analgesic effects of cannabis. In case reports (Noyes and Baram 1974), one young woman successfully employed cannabis to treat the pain and anxiety after a tubal ligation, and another in dysmenorrhea (p. 533): "The relief she got from smoking was prompt, complete, and consistently superior to that from aspirin."

In 1993, Grinspoon and Bakalar published *Marihuana, the forbidden medicine*, and subsequently revised it (Grinspoon and Bakalar 1997). The book contains numerous "anecdotal" testimonials from patients and doctors documenting clinical efficacy of cannabis where other drugs were ineffective. An entire section with case studies was included on premenstrual syndrome (PMS), menstrual

cramps, and labor pains, supporting excellent symptomatic relief at low doses without cognitive impairment.

Numerous surveys cite cannabis usage for obstetric and gynecological complaints, but in one Australian example, 51% of the women indicated indications for PMS or dysmenorrhea (Helliwell 1999).

Rätsch (1998) has observed (p. 162), "Several women who delivered their babies at home have told me that they smoked or ate hemp products to ease the painful contractions and the birth process in general."

Beyond direct effects mediated by the cannabinoid receptors, McPartland has proposed that therapeutic effects of cannabis in dysmenorrhea involve anti-inflammatory mechanisms (McPartland 1999, 2001).

It has been observed that women with PMS exhibit a fault in fatty acid metabolism that impedes the conversion of linoleic acid (LA) to gamma-linolenic acid (GLA) and prostaglandins. A daily dose of 150-200 milligrams of GLA over a twelve-week period significantly improved PMS-related symptoms (Horrobin and Manku 1989). As pointed out by Leson and Pless (2002), this amount of GLA can be supplied by only 5 ml of hemp seed oil daily.

Experimentally, Δ^9-THC inhibited herpes virus replication (HSV-1 and HSV-2) *in vitro*, even at low concentrations (Blevins and Dumic 1980), and was suggested for trials of topical usage.

An Italian group recently demonstrated the inhibition of proliferation of human breast cancer cells by anandamide *in vitro* (De Petrocellis et al. 1998); 2-arachidonylglycerol and the synthetic cannabinoid HU-210 acted similarly, while this activity was blocked by the CB_1 antagonist, SR 141716A. It was felt that these effects were mediated through inhibition of endogenous prolactin activity at its receptor. It is likely that THC acts similarly. Palmitylethanolamide has subsequently been demonstrated to inhibit expression of fatty acid amidohydrolase, thereby enhancing the antiproliferative effects of anandamide on human breast cancer cells (Di Marzo et al. 2001).

Recent animal work has elucidated the role of endocannabinoids in mammalian fertility. Recently Das et al. (1995) detected CB_1 receptor mRNA in mouse uterus, thus suggesting that this organ is capable of anandamide production. Anandamide (arachidonylethanolamide, AEA) and Δ^9-THC inhibited forskolin-stimulated cyclic AMP production in mouse uterus, whereas cannabidiol did not, suggesting that the uterine site is active in endocannabinoid production.

Schmid et al. (1997) demonstrated very high levels of anandamide in the peri-implantation mouse uterus. Data suggest that down-regulation of AEA levels promote uterine receptivity, while up-regulation may inhibit implantation. It was surmised that aberrant AEA synthesis or expression may be etiological in early pregnancy failure or infertility. The corresponding role that THC or canna-

bis may have in human females at the time of fertilization and implantation is open to conjecture, but deserves further investigation.

Wenger et al. (1997) claimed similarity in effects of injected THC and AEA in pregnant rats, prolonging length of gestation, and increasing stillbirths, perhaps due to inhibition of prostaglandin synthesis. The same lead author posited cannabinoid influences on hypothalamic and pituitary endocrine functions in a subsequent paper (Wenger et al. 1999).

Paria et al. (2001) suggested the need for tight regulation of endocannabinoid signaling during synchronization of embryonic development and uterine receptivity. They demonstrated inhibition of implantation in wild-type mice with sustained high-level exposure to "natural cannabinoid" while not in CB_1 (−/−)/CB_2 (−/−) double knockout mutant mice.

Issues of cannabis use in human pregnancy remain a great concern. The topic is reviewed in (Fried 2002; Murphy 2001; Zimmer and Morgan 1997). A variety of studies have demonstrated transient effects of cannabis on endocrine hormone levels, but no consistent effects seem to occur in chronic settings (Russo et al. 2002). Certainly subtle changes at critical times of fertilization or implantation may be significant. A valid assessment was provided (Murphy 1999, p. 379): "the hormone milieu at the time of exposure may dictate a woman's hormonal response to marijuana smoking."

Studies are hampered by the obvious fact that laboratory animals are not human in their responses. Estrous cycles and behaviors in animals are not always analogous to menstrual cycles and other physiological effects in women. Nevertheless, animal data suggest that in female rats, at least, THC acts on the CB_1 receptor to initiate signal transduction with membrane dopamine and intracellular progesterone receptors to initiate sexual responses (Mani, Mitchell, and O'Malley 2001).

One available approach to the issues is provided by examining factors in spontaneous abortions. In a study of 171 women, 25% of pregnancies ended spontaneously within 6 weeks of the last menses. Cannabis exposure seemed to have no observable effect in these cases (Wilcox, Weinberg, and Baird 1990).

The population of Ottawa, Ontario, Canada has been extensively examined over the last two decades with respect to cannabis effects in pregnancy. In a small study of cannabis using mothers vs. abstainers (O'Connell and Fried 1984), ocular hypertelorism and "severe epicanthus" were only noted in children born to users.

In 1987, the Ottawa group compared effects of cannabis, tobacco, alcohol and caffeine during gestation (Fried et al. 1987). Whereas tobacco negatively affected neonatal birth weight and head circumference, and alcohol was associated with lower birth weight and length, no effects on any growth parameters were ascribable to maternal cannabis usage.

In a subsequent study (Witter and Niebyl 1990), examination of 8350 birth records revealed that 417 mothers (5%) claimed cannabis-only usage in pregnancy, but no association was noted with prematurity or congenital anomalies. The authors suggested that previously ascribed links to cannabis were likely confounded by concomitant alcohol and tobacco abuse.

A group in Boston noted a decrease in birth weight of 79 g in infants born to 331 of 1226 surveyed mothers with positive using drug screen for cannabis ($p = 0.04$) (Parker and Zuckerman 1999), but no changes in gestation, head circumference or congenital abnormalities were noted.

The largest study of the issue to date evaluated 12,424 pregnancies (Linn et al. 1983). Although low birth weight, shortened gestation and malformations seemed to be associated with maternal cannabis usage, when logistic regression analysis was employed to control for other demographic and exposure factors, this association fell out of statistical significance.

Dreher has extensively examined prenatal cannabis usage in Jamaica (Dreher 1997; Dreher, Nugent, and Hudgins 1994), wherein the population observations were not compounded by concomitant alcohol, tobacco, or polydrug abuse. This study is unique in that regard, no less due to the heavy intake of cannabis ("ganja"), often daily, in this cohort of Rastafarian women. No differences were seen between groups of cannabis-using and non-cannabis-using mothers in the weight, length, gestational age or Apgar scores of their infants (Dreher, Nugent, and Hudgins 1994). Deleterious effects on progeny of cannabis smokers were not apparent; in fact, developmental precocity was observed in some measures in infants born to women who smoked ganja daily. The author noted (Dreher 1997, p. 168):

> The findings from Jamaica, however, suggest that prenatal cannabis exposure is considerably more complex than we might first have thought. Loss of appetite, nausea and fatigue compound the "bad feeling" that women in this study commonly reported. For many women, ganja was seen as an option that provided a solution to these problems, i.e., to increase their appetites, control and prevent the nausea of pregnancy, assist them to sleep, and give them the energy they needed to work. . . . The women with several pregnancies, in particular, reported that the feelings of depression and desperation attending motherhood in their impoverished communities were alleviated by both social and private smoking. In this respect, the role of cannabis in providing both physical comfort and a more optimistic outlook may need to be reconceptualized, not as a recreational vehicle of escapism, but as a serious attempt to deal with difficult physical, emotional, and financial circumstances.

DISCUSSION AND CONCLUSIONS

This presentation supports the proposition that cannabis has been employed historically for legion complaints in obstetrics and gynecology. To list briefly, these include treatment of: menstrual irregularity, menorrhagia, dysmenorrhea, threatened abortion, hyperemesis gravidarum, childbirth, postpartum hemorrhage, toxemic seizures, dysuria, urinary frequency, urinary retention, gonorrhea, menopausal symptoms, decreased libido, and as a possible abortifacient.

It is only recently that a physiological basis for these claims has been available with the discovery of the endocannabinoid system. Limited research to date supports these claims in terms of cannabinoid analgesia, antispasmodic and anti-inflammatory activities, but requires additional study to ascertain mechanisms and confounding variables.

Recommendations for cannabis therapeutics have often supported only utilization for terminal, intractable, or chronic disorders (Joy, Watson, and Benson 1999). However, simple logic would indicate that side effects of any medicine would be less evident when the agent is employed sporadically. Generally, that situation prevails for many of the listed Ob-Gyn indications for cannabis. Available historical and epidemiological data supports very low toxicity, even in pregnancy, to mother or child. Professor Philip Robson of Oxford has summarized the situation with cannabis in obstetrics nicely (Lords 1998, p. 123):

> If you could have an agent which both speeded labour up, prevented hemorrhage after labour and reduced pain, this would be very desirable. Cannabis is so disreputable that nobody would begin to think of that and yet that is really an obvious application that we should seriously consider with perhaps some basic research and pursue it.

A few intriguing issues remain. Is cannabis truly an abortifacient? Our four specific references are equivocal, one ancient (Darmesteter 1895), one old (Short 1751), and two modern (Merzouki, Ed-derfoufi, and Molero Mesa 2000; Merzouki 2001), but these and current epidemiological data would seem to indicate that cannabis does not produce this effect *sui generis*. Perhaps its actual role is one to *mitigate side effects* of the active components.

Numerous citations historically support the notion that cannabis is quite potent in its obstetric and gynecological actions, with specific attestation that medical benefits are frequently obtained at doses that are sub-psychoactive. The therapeutic ratio of cannabis with respect to cognitive impairment seems generous.

Another mystery worthy of additional study surrounds the very rapid activity claimed for cannabis extracts in promotion of labor (Grigor 1852; Christison 1851). Certainly modern anecdotal claims of a similar nature are legion when

cannabis is smoked. Pharmacodynamically, oral administration of extracts would be unlikely to provide benefits within minutes. Perhaps these tinctures were demonstrating a sublingual or mucosal absorption akin to those in modern trials of cannabis-based medical extracts (Whittle, Guy, and Robson 2001).

In summary, the long history of cannabis in women's medicine supports further therapeutic investigation and application to a large variety of difficult clinical conditions. Cannabis as a logical medical alternative in obstetrics and gynecology may yet prove to be, in the words of Robson (1998), a phoenix whose time it is to rise once more.

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Endocannabinoid Degradation and Human Fertility

M. Bari
N. Battista
A. Cartoni
G. D'Arcangelo
M. Maccarrone

SUMMARY. Anandamide (AEA) impairs mouse pregnancy and embryo development. Here, we overview the role of AEA in sexual function, focusing on AEA degradation during human pregnancy. Human peripheral lymphocytes express the AEA-hydrolyzing enzyme fatty acid amide hydrolase (FAAH), which decreases in miscarrying women. FAAH is regulated by progesterone and Th1/Th2 cytokines, whereas the AEA transporter and the AEA binding cannabinoid receptors are not affected. Taken together, our results appear to add the endocannabinoids to the hormone-cytokine array

M. Bari, BS, and N. Battista, BS, are Research Assistants, and M. Maccarrone, PhD (E-mail: Maccarrone@med.uniroma2.it), is Assistant Professor at the Department of Experimental Medicine and Biochemical Sciences, University of Rome "Tor Vergata," Via Montpellier 1, I-00133 Rome, Italy.

A. Cartoni, PhD, is Research Assistant and G. D'Arcangelo is Technical Assistant at the Department of Chemical Sciences and Technologies, University of Rome "Tor Vergata," Italy.

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involved in the control of human pregnancy, and suggest that FAAH might be a useful diagnostic marker for large scale, routine monitoring of gestation in humans.

KEYWORDS. Anandamide, cytokines, endocannabinoids, human fertility, sex hormones

INTRODUCTION

Endocannabinoids are an emerging class of lipid mediators, isolated from brain and peripheral tissues (Devane et al. 1992; Mechoulam et al. 1998), which mimic some of the psychotropic, hypnotic and analgesic effects of cannabinoids (Calignano et al. 1998; Meng et al. 1998). The latter compounds, and in particular Δ^9-tetrahydrocannabinol, were reported to have adverse effects on reproductive functions, including retarded embryo development, fetal loss and pregnancy failure (Das et al. 1995; Ness et al. 1999). A major endocannabinoid, anandamide (*N*-arachidonoylethanolamine, AEA), has been shown to impair pregnancy and embryo development in mice (Paria et al. 1996). Down-regulation of anandamide levels in mouse uterus has been associated with increased uterine receptivity, which instead decreased when AEA was up-regulated (Schmid et al. 1997). AEA is an endogenous ligand for both the brain-type (CB_1R) and the spleen-type (CB_2R) cannabinoid receptors, mimicking several actions of cannabinoids on the central nervous system and in peripheral tissues (Di Marzo 1998). CB_1R activation is detrimental for mouse preimplantation and development (Yang et al. 1996; Wang et al. 1999), but appears to accelerate trophoblast differentiation (Paria et al. 2000). A recent study has shown that sex steroids control the expression of the CB_1R gene in the anterior pituitary gland of both male and female rats, leading to the speculation that such a regulatory mechanism might be operational also in the reproductive organs (Gonzales et al. 2000). Moreover, the role of progesterone receptor in Δ^9-tetrahydrocannabinol modulation of sexual receptivity in female rats has been also demonstrated (Mani et al. 2001) and dysregulation of cannabinoid signalling has been shown to disrupt uterine receptivity for embryo implantation in mice (Paria et al. 2001). The effect of AEA via CB_1R and CB_2R depends on its concentration in the extracellular space, which is controlled by a two-step process: (i) cellular uptake by a specific AEA membrane transporter (AMT), and (ii) intracellular degradation by the AEA-hydrolyzing enzyme fatty acid amide hydrolase (FAAH). Since the first report showing an AEA-degrading enzyme (Deutsch and Chin 1993), AMT and FAAH have been characterized in

several mammalian cell lines (Di Marzo et al. 1999; Beltramo et al. 1997; Hillard et al. 1997) and more recently in human cells in culture, in brain (Maccarrone et al. 1998), in platelets (Maccarrone et al. 1999) and in mastocytes (Maccarrone et al. 2000a).

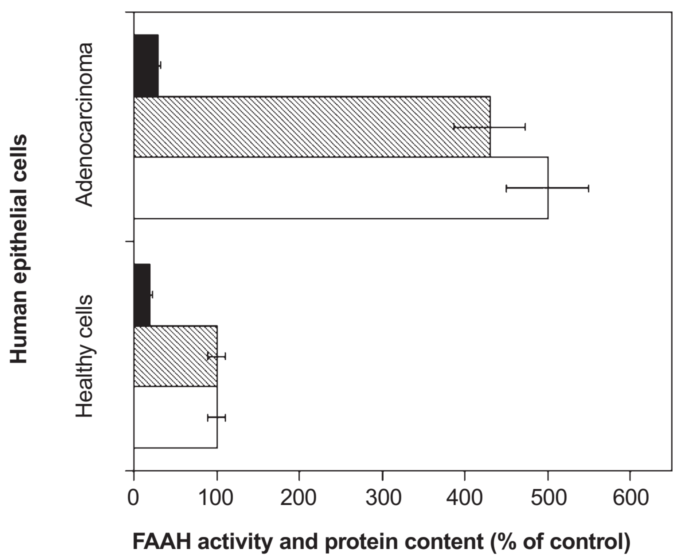
Despite the growing evidence that AEA adversely affects uterine receptivity and embryo implantation in mice (reviewed by Paria and Dey, 2000) and that AEA degradation by FAAH may have physiological significance in these processes (Paria et al. 1996; Paria et al. 1999; Maccarrone et al. 2000b), the regulation of FAAH during early pregnancy is still obscure. Recently, we observed down-regulation of FAAH expression in pseudopregnant mice, suggesting that FAAH modulation was independent of the presence of embryos in the uterus, and found that sex hormones like progesterone and estrogen down-regulate FAAH activity by reducing gene expression (Maccarrone et al. 2000b).

DISTRIBUTION OF FAAH AND AMT

FAAH was localized in the luminal and glandular epithelia of non pregnant mouse uterus (Maccarrone et al. 2000b). *In situ* hybridization consistently detected FAAH mRNA primarily in uterine luminal and glandular epithelial cells (Paria et al. 1999). Also human uterine epithelial cells had a remarkable FAAH activity, which increased more than five times in human adenocarcinoma cells (Maccarrone et al. 2000b). These findings, summarized in Figure 1, are consistent with an epithelial localization of FAAH also in the human endometrium. In this context, it is noteworthy that the Km values of FAAH from mouse or human uterus (approximately 7 μM) were comparable to those recently reported for human brain and for human neuroblastoma and lymphoma cell lines, whereas apparent Vmax values varied (Maccarrone et al. 1998; Maccarrone et al. 2000b). Therefore, it can be proposed that the same enzyme is differently expressed in various species or in different tissues of the same species. Sequence homology between rat, mouse and human FAAH genes (Giang et al. 1997) suggests that indeed FAAH gene is highly conserved. Therefore, the hormonal regulation of FAAH observed in mouse uterus might hold true also for the human counterpart.

FAAH activity was also demonstrated and characterized in mouse blastocysts (Maccarrone et al. 2000b). In order to be hydrolyzed by FAAH, AEA must be transported into the cell. Recent experiments performed on rat neuronal and leukemia cells (Bisogno et al. 1997), on human neuronal and immune cells (Maccarrone et al. 1998) and on human endothelial cells (Maccarrone et al. 2000c), clearly showed the presence of a high-affinity AEA membrane transporter (AMT) in the cell outer membranes. A similar AMT was found in mouse blastocysts (Maccarrone et al. 2000b). The affinity of this transporter was comparable to that of AMT in rat astrocytes (Km = 320 nM) (Beltramo et al. 1997) and

FIGURE 1. *FAAH activity and expression in human uterus*. FAAH activity (white bars) and content (hatched bars) were significantly increased in human adenocarcinoma cells compared to healthy epithelial cells. Antigen competition ELISA (black bars) validated the specificity of FAAH quantitation. 100% = 600 ± 50 $pmol.min^{-1}.mg\ protein^{-1}$ (activity) or 0.500 ± 0.050 A_{405} units (content).



human cells (Km = 130-200 nM) (Maccarrone et al. 1998). The blastocyst's AMT and FAAH might play a critical role in implantation, because nanomolar concentrations of AEA were found to inhibit embryo development and blastocysts hatching *in vitro* (Schmid et al. 1997; Paria et al. 1998; Maccarrone et al. 2000b). Both detrimental effects of AEA were inhibited by a CB_1R antagonist, in line with the hypothesis that they were mediated by this receptor (Yang et al. 1996).

AEA AND THE INDUCTION OF APOPTOSIS

Interestingly, AEA was found to induce apoptosis in blastocysts, and this effect was not prevented by CB_1R or CB_2R antagonists (Maccarrone et al. 2000b). This rules out the involvement of either cannabinoid receptor in the induction of programmed cell death by the endocannabinoids, and suggests that the arrest of embryo development and blastocyst hatching by AEA did not involve the deployment of apoptotic programmes (Afford et al. 1996; Tonnetti et al. 1999).

Consistently, AEA has been shown to inhibit cancer cell proliferation (De Petrocellis et al. 1998), and to induce apoptosis in lymphocytes (Schwarz et al. 1994), neuronal cells (Maccarrone et al. 2000d), and brain tumors (Galve-Roperh et al. 2000). These findings are in keeping with the notion that Δ^9-tetrahydrocannabinol promotes apoptosis in glioma cells, through a CB_1R independent mechanism (Sànchez et al. 1998).

Collectively, our findings lead to a general picture suggesting that a decreased FAAH activity in mouse uterus during early pregnancy might allow higher levels of AEA, which can be instrumental in modifying endometrium during pregnancy. However, the toxic effects of AEA to the blastocysts are prevented by the activity of AMT and FAAH in these cells, which rapidly scavenge the endocannabinoid. These events are under hormonal control, showing an interplay between endocannabinoids and sex hormones in regulating fertility in mammals. In this line, a recent report has demonstrated that FAAH promoter has a putative estrogen receptor binding site (Puffenbarger et al. 2001), further strengthening the concept of a common hormone-endocannabinoid network. From this stand-point, we sought to ascertain the role of endocannabinoid degradation in human fertility.

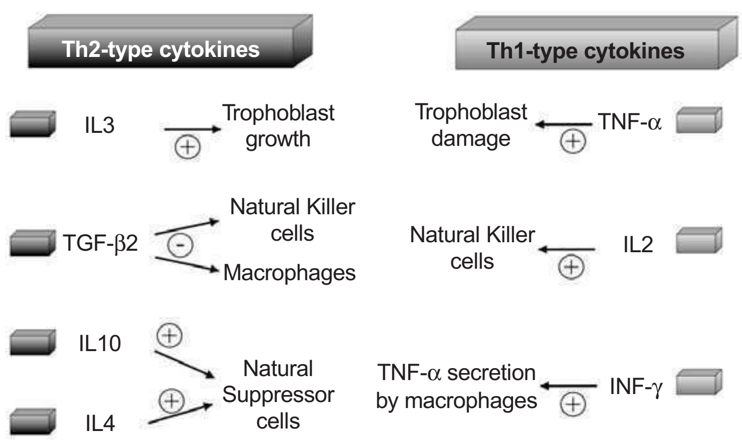
ENDOCANNABINOID DEGRADATION AND HUMAN FERTILITY

Spontaneous abortion is the most common adverse outcome of pregnancy, associated with considerable pain, suffering and medical costs (Kline et al. 1989; Sozio and Ness 1998). Early markers of miscarriage have long been sought for their clinical relevance, though they have not yet been identified (Goldstein et al. 1994; Redline et al. 1994). Little is known about the influence of lifestyle on spontaneous abortion, although cigarette smoking and the use of illicit drugs have been implicated as adverse factors (Walsh 1994; Ness et al. 1999).

Peripheral lymphocytes play a critical role in embryo implantation and successful pregnancy in humans (Piccinni et al. 1998). These cells produce leukemia inhibitory factor (LIF) and immunomodulatory proteins, which favor fetal implantation and survival (Szekenes-Bartho and Wegmann 1996; Stewart and Cullinan 1997; Duval et al. 2000). More generally, lymphocytes regulate a hormonal-cytokine network at the fetal-maternal interface, and a defect in the integrity of this network may result in fetal loss (Szekenes-Bartho and Wegmann 1996; Stewart and Cullinan 1997; Piccinni et al. 1998; Duval et al. 2000). Progesterone (P), a hormone essential for the maintenance of pregnancy, is also known to modulate immune function (Correale et al. 1998) and to elicit an immunological response critical for normal gestation (Szekenes-Bartho and Wegmann 1996; Szekenes-Bartho et al. 1996). Indeed, P has been shown to favor the development

of human T lymphocytes producing type 2 T-helper (Th2) cytokines (interleukins 3, 4 and 10, and transforming growth factor β2), which inhibit the anti-fertility Th1-type cytokines (tumor necrosis factor α, interleukin-2 and interferon-γ), thus allowing the survival of fetal allograft and successful pregnancy (Piccinni et al. 1995; Piccinni et al. 1996). The interactions between this cytokine network and the trophoblast are depicted in Figure 2. More recently, the P-induced Th2 bias has been found to stimulate the release of leukemia inhibitory factor (LIF) from T lymphocytes, mediated by IL-4 (Piccinni et al. 1998). Clinical data, showing that women with unexplained recurrent abortions have a reduced LIF production, suggest that the latter is indeed critical for implantation and maintenance of fetus in humans (Piccinni et al. 1998; Sharkey 1998; Taupin et al. 1999). FAAH might limit the pathophysiological effects of AEA and the other congeners by hydrolyzing them (Giang et al. 1997; Goparaju et al. 1998). Therefore, FAAH activity in lymphocytes might be involved in controlling pregnancy failure by regulating the level of AEA in uterus. In particular, it can be proposed that endocannabinoids may interfere with the lymphocyte-dependent

FIGURE 2. *Interaction between Th1/Th2 cytokines and trophoblast*. Type 2 T-helper (Th2) cytokines (interleukin (IL)-3, IL-4, IL-10 and transforming growth factor β2, TGF-β2) favor blastocyst implantation and successful pregnancy, by promoting, either directly or indirectly: (i) trophoblast growth, (ii) inhibition of natural killer (NK) cell activity, and (iii) stimulation of natural suppressor cells. Conversely, type 1 T-helper (Th1) cytokines (tumor necrosis factor α (TNF-α), IL-2, IL-12 and interferon (INF)-γ) impair gestation, by causing direct damage to the trophoblast, by stimulating NK cells and by enhancing TNF-α secretion by macrophages.



cytokine network which regulates the development and maintenance of successful pregnancy in humans (Piccinni et al. 1998).

FAAH IN MATERNAL LYMPHOCYTES AND HUMAN GESTATION

In this line, we have recently demonstrated that decreased activity and expression of FAAH in peripheral lymphocytes is an early (< 8 weeks of gestation) marker of human spontaneous abortion (Maccarrone et al. 2000e). Indeed, in a clinical study, we measured FAAH activity, [^{3}H]AEA uptake by AMT and [^{3}H]CP55.940 binding to CBR in lymphocytes isolated from 100 healthy women at 7-8 weeks of gestation (Maccarrone et al. 2001). This is the earliest time in gestation where the difference between FAAH content in women who miscarried and those who did not was found to be significant (Maccarrone et al. 2000e). The *a posteriori* association between the gestation outcome and the FAAH activity and expression, AMT activity or CBR binding, showed that FAAH activity and protein were lower in all the 15 women who miscarried than in the 85 who did not, whereas AMT activity and CBR binding were similar in both groups (Table 1). These observations point towards a key-role for FAAH, but not for AMT or CBR, in lymphocyte-mediated control of the hormone-cytokine network at the fetal-maternal interface. Since FAAH might indirectly control AMT, by maintaining the concentration gradient which drives AEA facilitated diffusion through AMT itself (Deutsch et al. 2001), it can be speculated that by controlling FAAH the cell controls also the transport of AEA, and hence its activity in the extracellular space. In this frame, we further investigated how FAAH might be regulated by fertility-related signal molecules.

We found that *in vitro* treatment of human lymphocytes with P, at the concentrations found in serum during pregnancy (from 0.02 to 0.30 µg/ml) (Piccinni et al. 1995), enhanced FAAH activity and gene expression in a dose-dependent manner, as did treatment of human lymphocytes with Th2-type cytokines IL-4 or IL-10. Conversely, treatment with Th1-type cytokines IL-12 or IFN-γ reduced FAAH activity and expression (Maccarrone et al. 2001). We also found that treatment of lymphocytes with P, IL-4, IL-10, IL-12, or IFN-γ did not quite affect AMT activity, neither did it affect [^{3}H]CP55.940 binding to CBR (Maccarrone et al. 2001).

High FAAH activity should lower the level of its substrate, and indeed in a following study we have shown that healthy women (with higher lymphocyte FAAH) have lower blood AEA compared to aborting patients (Maccarrone et al. 2002). As noted above, peripheral lymphocytes play a critical role in human pregnancy by producing LIF (Sharkey 1998). Therefore, we tested whether the endocannabinoids would affect LIF release from peripheral T cells. We found that

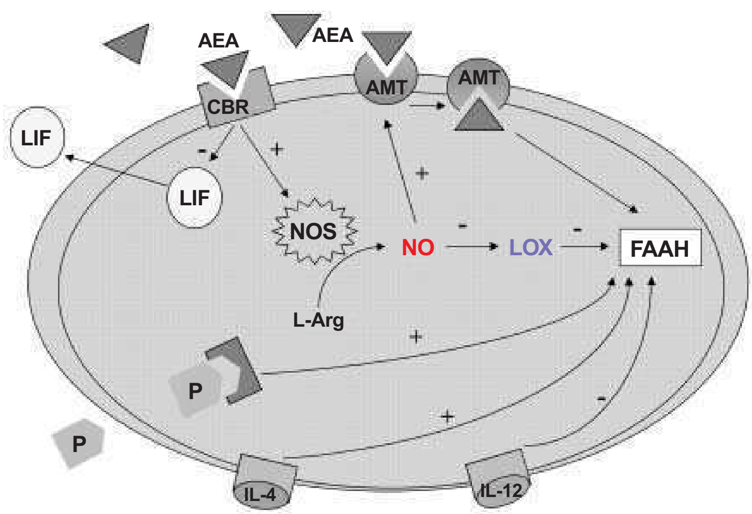
TABLE 1. CBR Binding, AMT Activity, and FAAH Activity and Content in Women Who Miscarried and Those Who Did Not

Parameter	Women with normal gestation	Women who miscarried
CBR binding	20380 ± 1930	20400 ± 1795
(cpm·mg protein^{-1})	(100%)	(100%)
AMT activity	50 ± 4	49 ± 4
(pmol·min^{-1}·mg protein^{-1})	(100%)	(100%)
FAAH activity	133 ± 9	48 ± 5
(pmol·min^{-1}·mg protein^{-1})	(100%)	(36%)
FAAH content	0.250 ± 0.030	0.130 ± 0.020
(A_{405} units)	(100%)	(52%)

treatment of human lymphocytes with AEA reduced the production of LIF, an effect counteracted by SR141716, but not by SR144528 nor by capsazepine, a selective antagonist of vanilloid receptors (Zygmunt et al. 1999). Therefore, inhibition of LIF release by AEA was mediated by CB_1 receptors only.

Altogether, these data suggest that a low FAAH activity, and hence higher AEA levels, can lead to spontaneous abortion by reducing LIF production. This unprecedented effect of AEA is consistent with its adverse effects on embryo implantation and development in mouse (Paria et al. 1996; Schmid et al. 1997; Yang et al. 1996; Di Marzo 1998; Wang et al. 1999; Maccarrone et al., 2000b). Moreover, keeping in mind the role of LIF in regulating growth and differentiation of neurons and endothelial cells (Taupin et al. 1999), a wider implication of the present findings can be anticipated. The interplay among P, cytokines, FAAH, endocannabinoids and LIF is depicted in Figure 3. It is shown that P, by interacting with its receptor, increases the synthesis of FAAH, which in turn reduces the extracellular concentration of AEA by driving its import through the AMT transporter. In this way the effect of AEA on LIF release by binding to type 1 cannabinoid receptors is reduced. FAAH activation by P is further enhanced by interleukin-4. This cytokine can also directly activate FAAH, as does interleukin-10, whereas interleukin-12 or interferon-γ inhibit FAAH activity. The scheme also shows that nitric oxide (NO), produced from L-arginine by CBR-activated nitric oxide synthase, stimulates AEA degradation, by (i) enhancing AMT activity (Maccarrone et al. 2000c), and (ii) preventing the inhibition of FAAH by lipoxygenase (Maccarrone et al. 1998; Maccarrone et al. 2000a). This is noteworthy, because of the manifold roles of NO in male and female fertility (Chwalisz and Garfield 2000; Kuo et al. 2000; Sikka et al. 2001; Herrero et al.

FIGURE 3. *AEA, progesterone and leukemia inhibitory factor in human lymphocytes.* Progesterone (P), by interacting with its intracellular receptor, increases the synthesis of FAAH, which in turn reduces the extracellular concentration of AEA by driving its import through the AEA membrane transporter (AMT). In this way the effect of AEA on leukemia inhibitory factor (LIF) release by binding to type 1 cannabinoid receptors (CBR) is reduced. FAAH activation by P is further enhanced by interleukin-4 or interleukin-10 (omitted for the sake of clarity), whereas it is partly prevented by interleukin-12 or interferon-γ (omitted for the sake of clarity). Also nitric oxide (NO), produced from L-arginine (L-Arg) by CBR-activated nitric oxide synthase (NOS), stimulates AEA degradation, by enhancing AMT and preventing the inhibition of FAAH by lipoxygenase (LOX) activity.



2001), thus adding a further player in the endocannabinoids/hormone/cytokine network regulating the reproductive function.

CONCLUSIONS

The reported findings give a biochemical ground to the previous observation that low FAAH activity correlates with spontaneous abortion in humans (Maccarrone et al. 2000e). They represent the first evidence of a link between the hormone-cytokine network responsible for successful pregnancy and the peripheral endocannabinoid system, and suggest that FAAH, but not anandamide transporter or CB receptors, might be critical for this link. These results might represent also a useful framework for the interpretation of a novel interaction be-

tween P and exogenous cannabinoids, recently shown to regulate female sexual receptivity (Mani et al. 2001). They also suggest that quantitation of FAAH protein in lymphocytes might be an accurate marker of spontaneous abortion in humans, easy to measure in routine analyses.

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Cannabinoids and Feeding: The Role of the Endogenous Cannabinoid System as a Trigger for Newborn Suckling

Ester Fride

SUMMARY. Cannabinoids are known to enhance appetite by activating cannabinoid (CB_1) receptors. This phenomenon is exploited to combat cachexia and loss of appetite in cancer and AIDS patients. The endocannabinoid 2-arachidonylglycerol (2-AG) is present in milk. Evidence is presented supporting a critical role for CB_1 receptors in survival of mouse pups. Thus neonates do not gain weight and die within the first week of life when their receptors are blocked. This is due apparently, to an inability to ingest maternal milk. This suggests that the endocannabinoid-CB_1 receptor system is unique in its absolute control over the initiation of the neonatal milk suckling response. It is further proposed that cannabis-based medicines should be developed to benefit infant failure to thrive.

Ester Fride, PhD, is Associate Professor, Department of Behavioral Sciences, and Head, Laboratory of Behavioral Biology, College of Judea and Samaria, Ariel, Israel 44837.

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ABBREVIATIONS. CB_1, cannabinoid 1, 2-AG, 2-arachidonylglycerol, CBD, cannabidiol

Cannabis is well known appetite stimulant (Abel 1971; Mattes et al. 1994; Fride 2002a). It is possible that the enhancement of appetite is selective for snack foods (Foltin, Brady, and Fischman 1986; Mattes, Shaw, and Engelman 1994). A role of the endocannabinoid system in the primitive invertebrate, *Hydra vulgaris*, has been demonstrated (De Petrocellis et al. 1999), thus pointing at a very widespread stimulatory role for cannabinoids in feeding. This, for most cannabis users, undesirable "side effect," has been clinically utilized for a number of years to combat a reduction in appetite and consequent weight reduction and wasting, as seen in conditions including AIDS and cancer (Mechoulam, Hanus, and Fride 1998). However, few controlled clinical studies have been performed (Bennett and Bennett 1999). In open pilot studies, dronabinol (Δ^9-THC) caused weight gain in the majority of subjects (Plasse et al. 1991). A relatively low dose of dronabinol, 2.5 mg twice daily, enhanced appetite and stabilized body weight in AIDS patients suffering from anorexia (Beal et al. 1997) for at least 7 months. In another study on AIDS patients, no weight gain was reported over the course of 12 weeks of dronabinol administration (2.5 mg twice a day), whereas a dose of 750 mg/day of megestrol acetate (a synthetic progestational drug), effected significant weight gain (Timpone et al. 1999). In that study, a high dose of megestrol (with potential adverse effects including dyspnea and hypertension), and a low dose of dronabinol were used. Higher doses of dronabinol may be more effective, although side effects such as weakness, confusion, memory impairment and anxiety, are a concern.

When dronabinol was administered to healthy volunteers, an increase in caloric intake was recorded after twice daily administrations for 3 days, when rectal suppositories were used, rather than the oral route (Mattes et al. 1994). When the effects of cannabis smoking by healthy volunteers on the intake of various types of food were compared, a selective increase in snack foods was observed (Foltin, Brady, and Fischman 1986). Thus the use of higher doses of cannabinoids as well as different routes of administration including the rectal (Bennett and Bennett 1999) or the sublingual (Whittle, Guy, and Robson 2001) route, should be further investigated.

Studies in laboratory animals have confirmed the human data, and unequivocally shown that cannabinoid 1 (CB_1) receptors mediate cannabinoid-induced increase in food ingestion (Williams and Kirkham 2002), especially of palatable

foods (Koch and Matthews 2001). Thus both exogenous cannabinoids (Δ^9-THC) and the endocannabinoid anandamide-induced enhancement of appetite were reversed by the specific CB_1 antagonist SR141716A (Williams, Rogers, and Kirkham 1998; Williams and Kirkham 2002). SR141716A injected by itself reduced appetite and body weight. Whether palatability is required for the antagonist's anorectic effect is controversial (Colombo et al. 1998; Freedland, Poston, and Porrino 2000; Arnone et al. 1997). In a chronic study in mice, very low doses of anandamide (0.001 mg/kg) were effective in enhancing food intake (Hao et al. 2000), in according with a stimulatory effect of very low doses of anandamide in a series of cannabimimetic assays (Sulcova, Mechoulam, and Fride 1998).

INTERACTIONS OF THE ENDOCANNABINOID SYSTEM WITH HORMONES REGULATING FOOD INTAKE

CB_1 receptors have been located in the hypothalamus (Herkenham et al. 1991; Mailleux and Vanderhaeghen 1992), a brain structure which is important in weight regulation. Although the precise mechanism by which cannabinoid receptors enhance appetite and food intake is not known, progress has been made in recent years to uncover such mechanisms (Mechoulam and Fride 2001). Thus Arnone et al. (1997) showed that the neuropeptide Y (NPY)-induced increase in sucrose drinking was inhibited by SR141716A, possibly linking this hormone, which is known to enhance food intake (Mechoulam and Fride 2001), to cannabinoid-stimulated appetite.

The hormone leptin is produced by fat tissue and is considered to be a key signal through which the hypothalamus senses the nutritional state of the body and helps maintain weight within a narrow range (Friedman 2000; Schwartz et al. 2000).

Within the hypothalamus, the arcuate nucleus contains neurons with receptors for two appetite-stimulating peptides (neuropeptide Y and agouti-related protein), as well as receptors for two peptides that reduce appetite (α-melanocyte-stimulating hormone and cocaine-and-amphetamine-regulated transcript). Leptin directly suppresses the activity of the two appetite-stimulating peptides, and stimulates the activity of the appetite-reducing ones, thereby decreasing appetite. Other molecules indirectly affected by leptin include melanin-concentrating hormone and a family of neuropeptides called orexins, which enhance appetite, as well as corticotropin-releasing hormone and oxytocin, which cause mice to eat less and to lose weight.

Di Marzo et al. (2001) have demonstrated that the endocannabinoid receptor system is an additional factor in this already complex weight-regulating system. Thus, when they administered leptin, the levels of the endocannabinoids anandamide and 2-arachidonylglycerol in the hypothalamus of normal rats were

reduced. Further evidence strengthens the idea that leptin down-regulates endocannabinoids. In a strain of obese rats in which leptin activity is impaired, the levels of endocannabinoids are higher than normal (Di Marzo et al. 2001). The same is true of obese *ob/ob* mice, which have an inherited lack of leptin, and of obese *db/db* mice, which have defective leptin receptors. Endocannabinoid levels are not affected in the cerebellum (which is commonly associated with motor coordination, but not with feeding) in these mice.

Taking together the human and animal studies, the effects of the cannabinoid system on food intake and appetite are significant, representing one of a multitude of players involved in this vital function.

ENDOCANNABINOIDS IN FOOD SUBSTANCES

The discovery of anandamide in chocolate (di Tomaso, Beltramo, and Piomelli 1996) raised the possibility that endocannabinoids contribute to the attractiveness of, and perhaps the intense craving for, this desirable food. Indeed, orally administered endocannabinoids (anandamide and 2-AG), albeit in very high doses, induced cannabimimetic effects in mice (Di Marzo et al. 1998). The very low amounts of anandamide found in cocoa powder and even lower concentrations in unfermented cocoa beans, would suggest the possibility that the anandamide in chocolate may be an artifact of processing (Di Marzo et al. 1998). Anandamide congeners that do not bind CB_1 receptors, including linoleoyl ethanolamide, oleoyl ethanolamide and oleamide ("sleep factor," Cravatt et al. 1995), all display cannabiminetic effects when applied *in vivo* (Fride at al. 1997), probably by inhibiting the fatty acid amide hydrolase (FAAH) enzyme which breaks down anandamide (see Fride 2002a). Oleamide, when given orally, displayed cannabimimetic effects in mice at doses several magnitudes higher than those present in chocolate, similar to orally administered anandamide (Di Marzo et al. 1998). Taken together, these results suggest that anandamide in chocolate, whether present in cocoa beans, or as an artifact of processing, could be responsible for any cannabinoid contribution to "chocolate craving." Future studies, testing anandamide and its congeners in more subtle behavioral assays such as "drug discrimination" or "place preference" designs may shed further light on the putative role for endocannabinoids in the rewarding effects of chocolate.

Interestingly, in the same study, and in a more recent one, relatively high concentrations of the endocannabinoid 2-AG but very low quantities of anandamide were detected in various types of milk (for instance, 8.7 ± 2.8 μg 2-AG/g extracted lipids from "mature" human milk). These concentrations of 2-AG were much higher than those found in other foods such as soybeans, hazelnuts and oatmeal (Di Marzo et al. 1998; Fride et al. 2001a).

DEVELOPMENTAL ASPECTS OF THE ENDOCANNABINOID-CB_1 RECEPTOR SYSTEM

Based on the findings described above, it is suggested that, as 2-AG is found in milk in significant amounts, this endocannabinoid must be of importance for the development of the newborn mammal. Several observations on developmental aspects of the endocannabinoid system in the central nervous system support such a hypothesis.

First, “atypical distribution patterns” of CB_1 receptors (i.e., a transient presence during development in regions where none are found at adulthood) were detected in white matter regions including the corpus callosum and anterior commissure (connecting neuronal pathways between the left and right hemispheres) between gestational day 21 and postnatal day 5, suggesting a role for endocannabinoids in brain development (Romero et al. 1997).

Further, although initial reports studying the development of the cannabinoid receptor system during the first weeks of postnatal life in the rat described a gradual increase in brain CB_1 receptor mRNA (McLaughlin and Abood 1993) and in the density of CB_1 receptors (Belue et al. 1995; Rodriguez de Fonseca et al. 1993), in later studies CB_1 receptor mRNA was also detected from gestational day 11 in the rat (Buckley et al. 1998). Additional studies have uncovered more complex developmental patterns. Thus, whereas the highest levels of mRNA expression of the CB_1 receptor are seen at adulthood in regions such as the caudate-putamen and the cerebellum, other areas such as the cerebral cortex, the hippocampus and the ventromedial hypothalamus display the highest mRNA CB_1 receptor levels on the first postnatal day (Berrendero et al. 1999; Fernandez-Ruiz et al. 2000). Finally, endocannabinoids were also detected from the gestational period in rodents, 2-AG at 1000 fold higher concentrations than anandamide. Interestingly, while anandamide displayed a gradual increase, constant levels of 2-AG were measured throughout development except for a single a peak on the first postnatal day (Berrendero et al. 1999).

Is it possible therefore, that the high levels of CB_1 receptor mRNA and 2-AG which have been observed on the first day of life in structures including the hypothalamic ventromedial nucleus (which is associated with feeding behavior) comprise a major stimulus for the first episode of milk suckling in the newborn?

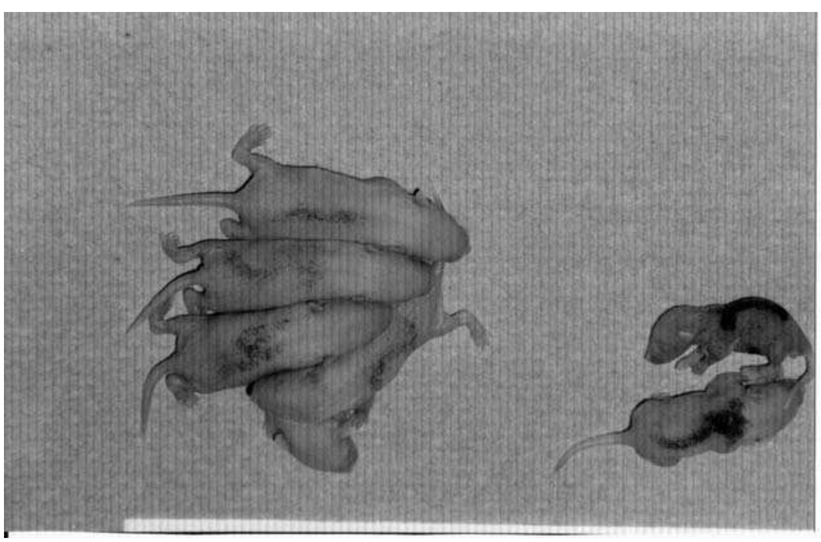
BLOCKADE OF CB_1 RECEPTORS IN NEWBORN MICE

Over the last few years, our group has investigated a role for the endocannabinoid system immediately after birth in mice. Administration of the specific CB_1 receptor antagonist SR141716A to the nursing mother had no effect on maternal weight, pup growth and development, or on maternal behavior (Fride,

Ginzburg and Mechoulam, unpublished observations). However, when CB_1 receptors were blocked by SR141716A in one day old pups by a single sc injection of SR141716A, a complete growth arrest and death within the first week of life was observed in virtually all SR141716A-treated pups (Fride et al. 2001a; Figure 1).

This devastating effect of SR141716A on the pups was dose-dependent (between 5-20 mg/kg). Furthermore, for the complete (almost 100% mortality) effect to take place, the antagonist had to be injected within the first 24 hours of life. Co-administration of Δ^9-THC almost completely reversed the effect, thus strongly suggesting that the SR141716A-induced effects were CB_1 receptor mediated. Co-administration of the endocannabinoid 2-AG did not reverse the SR141716A-induced mortality, presumably due to its rapid breakdown. However, 2-AG injected together with its "entourage" (fatty acid-esters which are always co-released with 2-AG, but which do not bind CB_1 receptors, and which counteract the breakdown and reuptake of 2-AG; see Ben-Shabat et al. 1998), significantly antagonized the growth-arresting effects of SR141716A on the pups (Figure 2). Subsequent experiments designed to further support the specificity of the CB_1 receptor in the mediation of the antagonist-induced pup mortality indi-

FIGURE 1. Five day old vehicle-injected (left) and SR141716A-injected (right) mouse pups. Pups, from the same litter, were injected sc (10 µl/g) within 24 hr after birth with vehicle (ethanol:emulphor:saline = 1:1:18), or SR141716A (20 mg/kg).

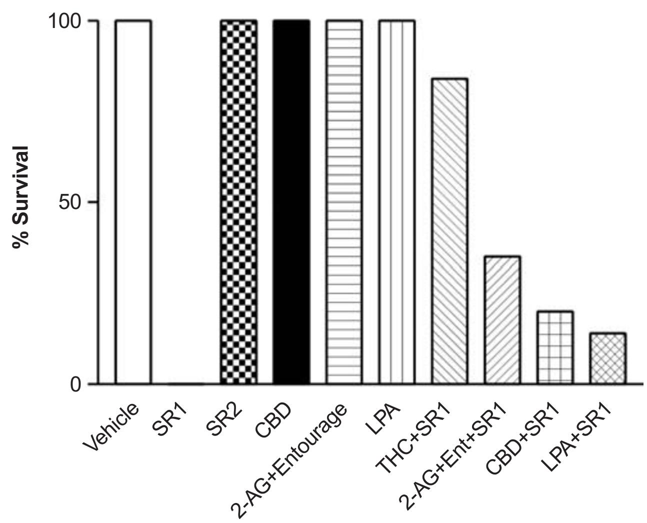


cated that cannabidiol (CBD), the non-psychoactive, non-CB_1 receptor binding cannabinoid, did not reverse the effects of SR141716A (Fride et al. 2001a; Figure 2), while the CB_2 receptor antagonist, SR144528, did not affect pup growth (unpublished observations).

MECHANISMS OF THE CB_1 RECEPTOR BLOCKADE-INDUCED GROWTH STUNTING EFFECTS

An initial investigation of possible mechanisms involved in sequelae of CB_1 receptor blockade in pups suggested that maternal behavior toward SR141716A-injected pups was not adversely affected. On the contrary, the dams spent significantly more time "licking" and nursing the antagonist-treated pups (Fride et al. 2001a). Rather, the CB_1 receptor blockade on day 1 of life disables the ability of the newborns to initiate milk suckling, as their stomachs were empty of milk (Fride et al. 2001a).

FIGURE 2. Summary of survival rates in pups one week after birth after various treatments on day 1 of life. SR1 = SR141716A (20 mg/kg), SR2 = SR144528 (20 mg/kg), CBD = cannabidiol (20 mg/kg), Entourage = palmityl glycerol (5 mg/kg) and lineoyl glycerol (10 mg/kg); these were added to the injection of 2-AG (1 mg/kg). LPA = lysophosphatidic acid (18:1, n-9, 20 mg/kg). All compounds were injected sc in the neck or flank in volumes of 10 μl/g.



More recent evidence for the role of CB_1 receptors in milk suckling is derived from CB_1 receptor-deficient ($CB_1^{-/-}$ knockout) mice, where it was observed that the CB_1 receptor antagonist had significantly less severe effects on the $CB_1^{-/-}$ pups, as compared to the effects on wild type mice (Fride et al., in preparation).

Lysophosphatidic acid (LPA) is a multifunctional lipid mediator with growth factor-like properties. LPA occurs in brain in considerable concentrations and is structurally similar to the endocannabinoid 2-AG. The LPA and CB_1 receptors display substantial (30%) homology. LPA, with 2-arachidonic acid as the acyl moiety, differs only by the absence of a phosphate group from 2-AG while a related lysophosphatidic acid (with 1-arachidonic acid as the acyl moiety) has been detected in rat brain (Sugiura et al. 1999). A defective suckling response was reported in neonatal mice that have a targeted deletion of the gene for the LPA receptor (lp_{A1}) (Contos et al. 2000). Our group therefore investigated the possibility that LPA and 2-AG may interact at their receptors. If the inhibition of milk ingestion in our experiments were due to an interaction of the CB_1 antagonist at the LPA receptor, or alternatively, if LPA interacts with the CB_1 receptor, then co-application of LPA with SR141716A on newborn pups should reverse the antagonist inhibition of pup development. This was not the case in our experiments. Thus, when LPA was co-injected with SR141716A, only a temporary delay in mortality, with borderline significance ($p = 0.09$), was observed (Fride, Rosenberg, and Mechoulam 2001b). Moreover, LPA did not bind to CB_1 receptors (Hanus and Fride, unpublished observations). Since the LPA employed contained oleic acid as the acyl moiety, and not arachidonic acid (which can not be obtained commercially), further investigation of the interaction between the LPA and CB_1 receptor systems is warranted.

Several neuroactive substances have been implicated in milk suckling. For example, Smotherman and colleagues (Petrov, Varlinskaya, and Smotherman 1998) have demonstrated an inhibition of several components of the suckling response after injection of naloxone into the cerebral ventricles of rat pups. When effects of intracisternal injections of a specific μ opiate receptor antagonist on weight gain were recorded, only a slight, transient reduction was seen; similar injections into the cerebral ventricles did not have any effect on body weight (Petrov et al. 1998).

Taken together, our studies argue for a critical role for CB_1 receptor activation in milk suckling in the newborn, presumably by 2-AG produced by the neonatal brain. As far as is known, the endocannabinoid-CB_1 receptor system is the first neural system discovered thus far that seems to display complete control over milk ingestion and neonatal survival.

CONCLUSIONS

Our data have indicated that the CB_1 receptor antagonist had to be injected within 24 hr after birth of mouse pups in order to produce a virtual 100% mortality effect (injection on day 2 resulted in less than 50% mortality). It is proposed that without CB_1 receptor activation by 2-AG (or another as yet undefined endocannabinoid) within the first 24 hr of life, the first suckling episode is not initiated. As the pups have not suckled yet, the source of this 2-AG must be the pup's brain, and not maternal milk. This is compatible with the surge of 2-AG and CB_1 receptor mRNA in the 1-day old rat brain (Berrendero et al. 1999; Fernandez-Ruiz et al. 2000). The lower levels of 2-AG and CB_1 receptors present from day 2 onward are apparently too low, or too late, to allow the suckling response to be initiated on subsequent days.

These observations further suggest that the enhancement in appetite and food intake induced by cannabinoids in the adult organism may only be the tip of the iceberg of the vital role for the cannabinoid system in milk suckling immediately after birth (Fride et al. 2001a). The comparatively more partial control of the endocannabinoid system of appetite and food intake by the mature organism should not diminish our efforts to develop cannabis-based medicines for appetite stimulation in conditions involving cachexia. Rather, it does suggest that treatment of children suffering such conditions may benefit at least as much as adults from cannabinoids to combat anorexia (Fride 2002b). Further, treating infants suffering from a failure to thrive with cannabinoid-derived medicines deserves future research.

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Hyperemesis Gravidarum and Clinical Cannabis: To Eat or Not to Eat?

Wei-Ni Lin Curry

SUMMARY. Hyperemesis gravidarum (HG), a debilitating ailment characterized by severe nausea and vomiting, malnutrition, and weight loss during pregnancy, occurs to 1-2% of pregnant women globally. Although the medical community offers clinical and pharmaceutical intervention, the procedures are: (1) partially effective, if at all, (2) costly and unaffordable without health insurance, (3) questionable in their long-term safety for the fetus, as most have not been scientifically tested, and (4) in more severe cases, physically painful and psychologically disempowering for the pregnant woman. This study unveils the deep suffering endured by women undergoing HG from a folkloristic perspective and proposes the use of medical cannabis as an effective natural remedy for the symptoms of HG. Due to the criminalization of cannabis and the stigma of its use during pregnancy, no formalized testing has been conducted, thus far, to investigate such a claim. While a small, underground, pilot study of cannabis treatment for HG has proven relatively promising, clinical trials are necessary for a more conclusive answer. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

Wei-Ni Lin Curry, MA, is a PhD student at UCLA and is affiliated with the UCLA/Folklore Program and Archives, 1075 Public Policy Building, Box 951459, Los Angeles, CA 90095-1459 (E-mail: wcurry@ucla.edu).

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The ideal pregnant woman radiates the image of a full-fleshed, well-nourished femininity whose presence glows of maternal well-being and ripeness. She is commonly encouraged by her family and friends to eat in increased proportions because the accepted consensus is that she is "eating for two." Her circle of loved ones will often assist her in fulfilling her food cravings. It matters not that she fancies strange foods, demands unappealing concoctions, or eats during the most unpredictable and indiscriminate times of the day (Murcott 1988). What matters is that she eats well. However, what happens when she is *unable* to eat for two? What happens when she *cannot eat for even one?*

While such a debilitating illness does not often occur, it happens to pregnant women who suffer from a disease known as *hyperemesis gravidarum* (HG) (Erick 1997; Van de Ven 1997). HG to a pregnant woman is similar to the wasting syndrome of an AIDS sufferer or a cancer chemotherapy patient whose body becomes severely emaciated, dehydrated, and malnourished due to persistent, uncontrollable vomiting and the inability to eat and drink (Grinspoon 1997). A striking difference, however, is that the survivor of HG carries the added responsibility of sustaining another life within her womb. While she perishes from hunger, her baby *in utero* continues to absorb any remains of stored fat, muscle tissue and nutrients from her body in order to survive. Compared to the weight loss endured by those undergoing AIDS or cancer chemotherapy, the HG woman's shedding of pounds is deceptively unsparing as her baby's continual growth and weight-gain disguises the actual body mass she is really losing. In essence, a pregnant woman with hyperemesis does not come anywhere near *eating for two*; she is more accurately *starving for two.*

HG, ITS MEDICALIZATION, AND THE SURVIVORS

Hyperemesis gravidarum is conservatively defined in *The Harvard Guide to Women's Health* (1996) as a debilitating condition of severe nausea and vomiting during pregnancy, resulting in malnutrition, dehydration, and weight loss. While women experience various degrees of HG, the prolonged retching and starvation often trigger the onset of other physically disabling ailments such as, but not limited to, partial paralysis, failed muscle coordination, ruptured esophagus, bloody emesis and/or stool, hemorrhage of the retina, inflamed pancreas, and/or wasting

of muscle tissue. In rare cases, HG has also been associated with coma, temporary blindness, and even death (Hillborn et al. 1999; Tesfaye et al. 1998).

The following personal anecdotes of real women bring into perspective the devastation and symptoms of starvation caused by HG: "Sarah" stated, ". . . I lost a total of 30 pounds and I was skinny to begin with. I was a walking skeletal with a belly. I looked like death and smelled like poison." "Sofia" said, "With my son [first pregnancy], I just got very ill from the point the sperm met the egg. I lost 30 pounds within the first 2 months, and I stayed in bed the whole 9 months, only getting up to use the restroom." She also observed, "[second pregnancy] I was throwing up first the acid in my stomach, which is yellow, then it's orange because it's the outer layer, and then you get to the green bile which is [from] your intestines. Then once you're past that, you go straight blood."

With her first pregnancy, Sofia was at least able to swallow and digest one burrito as her entire weekly sustenance. By her second pregnancy, however, food was definitely not an option. Sofia explains:

> I knew within one week of the conception that I was pregnant. Immediately vomiting and loss of appetite. *I couldn't swallow my own spit* for the first five months of my pregnancy . . . Within the first two weeks of my pregnancy, [I was hospitalized] twice. I would have five days that I could survive at home, then I would get so dehydrated that I'd have to go to the hospital to the ER so that I could get hydrated. I'd stay in the hospital one to two days. They'd get me fully hydrated, and then they'd send me home.

Also, Sofia's attempt at the traditional folk-remedy of soda and crackers resulted in vomiting: "The doctors thought that it was all in my head–thought that I was *bulimic*." The doctors intravenously injected units of fluid into her body in an attempt to increase her caloric intake. She grimaces: "They were feeding me lard. It *smelled* like lard. It *smelled* like grease."

One who physically experiences the starvation and nausea of hyperemesis gravidarum will often encounter psychological and emotional distress. The hormonal changes and mood fluctuations that are often associated with a normal pregnancy inevitably become more severe with the onset of HG (Simpson et al. 2001). In struggling to bear her child, the HG mother must also brace herself through such symptoms as depression, unnatural fatigue, amnesia, apathy, distorted body image, fear, and/or guilt (Erick 1997; Hillborn et al. 1999; Tesfaye et al. 1998). Some even contemplate suicide, as each living moment is excruciatingly taxing and painful:

> *I wanted to die every waking hour.* I thought I was in hell. Doctors told me that I was trying to orally vomit my baby out, that the pregnancy was not wanted. They sent me to psychiatrists claiming that all this was "in my

> head." Nobody understood me. My husband even left me. I was all alone with my tortured body, praying to God to give me strength to go on. (Sarah)

> *I . . . just wanted to die every minute that I was awake.* I still consider it a miracle that I and (more importantly) my two healthy children survived. I was *depressed* throughout the pregnancies as well as from not being able to take care of my two-and-a-half year old when I was pregnant with the second. I shudder when I think about it . . . (Julia)

> *I'd cry every night* . . . I feel that I'm a very strong individual, but this was no time to be strong. I'd cry every night, telling my husband how it hurt so bad. (Sofia)

A substantial number of HG survivors are also left with no choice but to cease employment and, if needed, temporarily relinquish the custody of their children to a more capable caregiver, such as a relative or a friend. Sofia solemnly recalls that when she was pregnant with her second child, she had to drop out of college where she was a student; she also had to give her mother legal guardianship of her seven-year-old son for the entire pregnancy, "Because I couldn't even cook or clean my own body, I couldn't do it to my own child. *And I wouldn't want him to be subjected to see me the way that I was.*"

Sadly enough, physical disability and the continual and frequent visits to the hospital for vital replenishment often isolate the HG woman from the warmth and comfort of her family and home during a time when she needs support the most.

While general nausea and vomiting, better known as morning sickness, is experienced by 70% to 80% of all pregnancies, only 1-2% is affected by the pernicious emesis and distress associated with hyperemesis gravidarum. Of this HG populace, 5% endure the debilitating symptoms for the entire nine-month period of their infant's gestation (Van de Ven 1997). Statistics taken in 1993 reveal that within one year, 42,000 women in the United States sought the help of a health care professional in an effort to counteract their symptoms of HG. In Britain, a study also shows that two of every one hundred HG mothers will opt for abortion, most likely, as a last resort to terminate their unbearable suffering and not the lives of their often much wanted unborn babies (Erick 1997). Sarah, who aborted against her will, grieves:

> Two weeks ago, I terminated my very much wanted pregnancy because of hyperemesis gravidarum. This disease is so disgusting and nightmarish, I don't know how I was able to do it the first time around. *I regret the abortion* but I just have to think about HG and remember the ordeal I went through and don't want to go through again . . . Before my abortion, I was prescribed Diclectin® [a Canadian combination of vitamin B_6 and the anti-

> histamine, doxylamine], four doses a day. It didn't help. I just wish there was a cure for this disease because *I want my baby back!*

Sofia chose not to abort, even at the strong recommendation of medical professionals and loved ones:

> [When] I was five months three weeks pregnant sitting in the UCSD Medical Center for the umpteenth time, I had the chief of staff, my personal ob/gyn was a chief resident, and three other specialists–whether they be the gastro-intestinal specialist and a couple of other ones–there'd be around six or seven other specialists standing around my bed. They all came to the conclusion that I needed to abort . . . I just told them I've survived five months and three weeks, why couldn't I survive two more months?

Other women adamantly refuse to consider abortion on grounds of their moral paradigm.

While many women and infants throughout history have died due to HG, prenatal mothers in industrialized, metropolitan areas are usually spared such a fatal outcome with the assistance of approved medical modalities. Western physicians prescribe anti-emetic pharmaceutical drugs, such as metaclopramide (Reglan®), prochlorperazine (Compazine®), promethazine (Phenergan®), and ondansetron (Zofran®), to help mothers keep their nausea at bay and nourish themselves and their fetuses. The drugs, which are also commonly given to AIDS and cancer chemotherapy patients, are taken orally, intravenously, or as rectal suppositories. While the long-term risks to the human child *in utero* remains unknown, the general consensus from the medical establishment is that the risks to the mother and fetus of severe morning sickness warrant possible risks of using these drugs during pregnancy (Carlson et al. 1996). At the very least, the babies who have ingested these medications via the placenta have been born comparatively healthy; none have emerged from the womb with birth defects, as did the infant casualties of thalidomide, the pharmaceutical drug given to mothers in the 1950s to alleviate indications of morning sickness and HG.

Nevertheless, the drugs are not fail proof. According to the Summary of Data on Hyperemesis Gravidarum (Schoenberg 2000), some of the most common antiemetic medications and the safety ratings that were assigned to them by the Food and Drug Administration (FDA) are listed as follows: ten drugs (scopolamine, promethazine, prochlorperazine, chlorpromazine, trimethobenzamide, cisapride, droperidol, coricosteroids, ondansetron, and hydoxyzine) received the rating of C, six drugs (doxylamine, diphenhydramine, cyclizine, meclizine, dimenhydrinate, and metaclopramide) received the rating of B, and one drug (pyridoxine, vitamin B6) received the rating of A. A C-rating means "animal studies show risk but human studies are lacking, or there are no studies in humans

or animals." A B-rating means "animal studies show no risk but human studies are inadequate, or animal studies show some risk but the risk is not supported by human studies." An A-rating signifies "no fetal risk" (Schoenberg 2000). Apparently, all the drugs listed, with the exception of one, a vitamin, are questionable in their safety, posing a potential threat to the fetus. Unsurprisingly, these pharmaceutical drugs threaten the mother, if not the baby, with many side effects and harmful allergic reactions. Sofia recounts her experience with the anti-emetic drugs–prochloperazine, metaclopramide, and promethazine, before she had to suspend her student status at her university due to HG:

> Well, the second week [of pregnancy] I was taking all three [medications]. I was sitting in lecture hall, and my body began to convulse. And literally, like an *epileptic seizure,* my tongue was upside down, my back was out of whack, [and I] couldn't control my legs or my arms. My husband conveniently was visiting me that day, and was in lecture hall with me. He had to pick me up and take me to the ER.

From that point onward, Sofia was unable to take any medications for her nausea and vomiting. It was not until she was in her sixth month of pregnancy that she was given another, ondansetron. She was discouraged from taking the drug any earlier because the doctors were uncertain of the possible side effects. Another fellow-student and HG survivor, Nora, has also professed to me that if she ever became pregnant again, she would not want to take any medications because they made her feel "drugged out" and "like a zombie" all day.

Because the modern anti-emetic medications have not succeeded in eliminating all symptoms of vomiting and nausea, and fail to stimulate the woman's appetite, mothers with hyperemesis continue to struggle with eating and maintaining (if not gaining) weight. Hence, within the framework of modern medicine, a crucial part of the women's survival relies on intake of liquid nutrition through tubes: intravenously, nasogastrically, or enterally, and often without the use of anesthesia. In certain situations, a gastrostomy tube is required for the purpose of drainage and decompression. Some may suffer from what Sofia calls a "collapsed digestive system." She noted, "[The doctors] were worried that all my organs were going to shut down, because I wasn't using them. I . . . [was having] *bowel movements maybe once every two months . . . I had no food. I had no intake*. I just didn't need to go."

To this day, six years after the birth of her daughter, Sofia is unable to digest a regular meal; unless she divides a single portion into two or three smaller servings, and unless she avoids anything too meaty, greasy, or rich, she will vomit shortly after consuming the food.

Sofia also braved the tortures of having intravenous tubes continually inserted and re-inserted into her body due to life-threatening blood clots that periodically

developed as a result of being fed liquid nutrition. Sofia said that even though the nurses were administering heparin through her IV to achieve anticoagulation, the blood clots continued to recur. She recounts:

> I was around seven months pregnant when that one [about the eighth tube inserted] went bad with a blood clot close to my neck. [The doctors] immediately said, *"We need to take it out."* But they didn't know what they had done inside. There were *roots* growing all along, all around the tubes inside of my chest because all the scar tissue that had formed. And the doctor, when he was taking it out, was literally *pulling* it–mind you, I had NO ANESTHESIA, and I was in PAIN!

At this point, I could not resist interrupting her to make sure I was hearing correctly, asking: "So he basically *tore your flesh*?"

> *YES.* And when it didn't come out, he had to stick scalpels in through these bottom holes, and try to tear away the scar tissue underneath. Yeah. And my husband had to sit there and tell me everything is *"okay–don't worry, it doesn't look that bad."* But after the fact, he was like, *"I was just trying to give you moral support. That ASSHOLE was tearing you apart and I was watching every minute of it."*

Sofia emphasizes that throughout her pregnancy she had "really bad scabs everywhere." She said she looked like a *"druggy."* Just the one surgical procedure left an open, gaping wound "about the size of a quarter" above her chest for nearly a month. Unfortunately, these scars will remain with her for the rest of her life, physically and emotionally.

Sofia is one of many women whose flesh and blood are sacrificed at the price of HG medical treatments. Another hyperemesis sufferer ("Mary") is highlighted in a dietician's case study that explains the woman's struggles with receiving liquid nutrition throughout her pregnancy (Erick 1997). I have paraphrased the case. When Mary was first admitted to the hospital, she was severely malnourished and dehydrated due to HG. The hospital began medical treatments by administering an IV feeding tube for her, but it was unsuccessful due to continued malnutrition. A nasogastric tube followed. Mary vomited three of the tubes in a two-day period, so she refused further replacements. The doctors then tried a different route via a jejunostomy and gastrostomy tube, one for feeding and the other for drainage. This method remained until the time of her delivery. However, for the entire pregnancy, Mary continued to vomit in spite of anti-emesis medications. The smell of the liquid formula used for her enteral feedings also increased her nausea. Mary also continued suffering from insomnia, pancreatitis, increased bloating, abdominal pain, chest pain, thick phlegm, depression, and a distorted body

image. Her partner was said to have shown disgust with the presence of the tubes sticking out of her body. Finally, she *threatened suicide* if she was not delivered immediately. A cesarean operation was performed before the expected date of delivery, as well as a permanent sterilization, done at her request. The baby was born relatively healthy at 6.45 pounds.

The story of Mary's struggles to feed herself and her baby through the devastating symptoms of HG cries for empathy and compassion. Though her doctors were most likely sincere in their intentions to keep her sickness under control, and though they succeeded in saving the life of the infant, I wonder if they realize how truly horrific their treatments really were? To what extent did they help Mary and to what extent did they hurt her, physically and psychologically? How much did they contribute to her experience of a healthy and dignified pregnancy, one that every woman deserves? Alternatives are in dire need.

Because many HG patients have shown that their nausea and vomiting are "linked to the consumption of food," the administration of liquid nutrition via feeding tubes is justified by doctors; it is argued that in sparing HG women from the physical act of smelling, masticating, and swallowing their meals, their nausea and vomiting will decrease (Van de Ven 1997). Unfortunately, in the case of both Sofia and Mary, their vomiting was triggered by the smell of the liquid formula.

The causes of hyperemesis have provoked heated speculation, but no substantial evidence has been discovered or acknowledged within the Western medical hegemony. Some scientists hypothesize the following as factors that often lead to and/or are connected to HG: hormones, increased estrogen level, nutrition, thiamine deficiency, psychological factors (Simpson et al. 2001) and the sex of the child, higher concentration of human chorionic gonadotropin level associated with a female fetus (Askling 1999; Panesar et al. 2001). As none of the factors offer a satisfactory answer, HG remains a perplexing female mystery for the present-day medical establishment. The frustration is mostly felt by women who are survivors of HG, desperately searching for a cure and increased understanding of this harrowing disease:

> I have suffered through two pregnancies with this debilitating condition . . . In both pregnancies, it started at six weeks and continued until the baby was born. I was induced early both times because I was so sick. I tried everything: hypnosis, homeopathic treatment, acupuncture, sea sick bands, IVs, smelling ginger and lemons, Compazine®, Reglan®, Phenergan®, Atavan®, Unisom®, Zofran® (to name a few). Nothing worked. I threw up constantly, including a lot of bile and dry heaving, could barely walk and just *wanted to die every minute* . . . It is extremely frustrating how little research and ideas exist on the topic, and I feel quite confident that if men could experience the condition, there would be a remedy for it. (Julia)

The medical establishment must begin to realize that even though the HG woman is unable to eat, the only thing she really wants *is* to eat.

The HG sufferer is not simply a lifeless, unfeeling, docile body (Foucault 1995) that robotically pumps vitamins and minerals into her growing child. She is a human being who needs to eat to live. Her ability to savor her meal, to salivate, to masticate, to swallow, to digest, is a primal and essential part of her existence. The woman with hyperemesis needs more than feeding tubes and synthetic liquid nutrition. She craves and requires real food, just like her baby needs a mother, and not a machine.

CANNABIS, PREGNANCY, AND HG

I, too, am a survivor of hyperemesis gravidarum. While I suffered through severe morning sickness my first pregnancy, it was not until my second pregnancy that I experienced the merciless symptoms of life-threatening HG. Within two weeks of my daughter's conception, I became desperately nauseated and vomited throughout the day and night. Every time I attempted to eat or drink *anything*, even water, I would immediately throw it up. Because nothing would stay in my stomach, I lost twenty-one pounds within the first two weeks of hyperemesis, which was over 20% of my normal body weight at the time (105 pounds). I vomited bile of every shade, and soon began retching up blood. I was also bleeding out of my vagina due to the pressures from vomiting, and owing to the fact that my vulva was still weak from two surgeries to remove cervical cancer after my first pregnancy.

I felt so helpless and distraught that I went to the abortion clinic twice, but both times I left without going through with the procedure. My partner and my three-year-old son feared for my life. My son would often ask me, with tears streaming down his face: "Mommy, are you going to die?" Each time, I reassured him that mommy would be okay soon, but he was not convinced. Could I blame him? I felt as if my whole world was falling apart, and that the ones I loved most were being dragged down with me. I tried desperately to function as usual, to work, cook, clean, care for my son, but all of my usual duties had to be sacrificed as I spent my entire day retching into the toilet, where I would often pass out because I had no energy to walk to and from the bathroom.

When I went to an obstetrician in search of help, the options he gave me were the usual: hospitalization, intravenous feedings, and anti-emesis pharmaceutical drugs that had unknown long-term side effects with the potential of affecting my child negatively. Instead, I tried ginger, raspberry tea, soda and crackers, acupressure, meditation, all the recommended home remedies, but nothing worked. Finally, I decided to try medical cannabis. The medical cannabis initiative, The Compassionate Use Act of 1996, which had been passed by the voters of Califor-

nia, permits the legal use of cannabis for the severely ill. If cannabis had been so effective in alleviating the nausea and vomiting for AIDS and cancer chemotherapy patients, then why would it not work for pregnant HG patients? I asked a Harvard physician, Lester Grinspoon, who had been studying the therapeutic properties of cannabis for the past thirty-some years. He said that other women throughout history and in modern times have used cannabis for HG and experienced positive results. With his reassurance, I felt more confident in attempting to remedy my sickness with the herb.

Because I had never smoked before, I first had to learn to take the medicine, but that was a welcome task, seeing that the herb worked wonders. Just one to two little puffs at night, and if needed in the morning, resulted in an entire day of wellness. I went from not eating, not drinking, not functioning, and continually vomiting and bleeding from two orifices to being completely cured. The only HG symptom that persisted was my acute sense of smell, which in the absence of nausea and vomiting was tolerable. Not only did I eat and drink, I consumed food with a hearty and open appetite.

The cannabis worked so miraculously that at first I thought my mind was playing tricks on me, as if I was being deceived by some placebo effect. In order to test, I stopped taking the cannabis three times, and each time the uncontrollable and violent retching returned. Finally, my son, who was three years old at the time, begged me: "Mommy, *please* go take your medicine!" That was when I knew that cannabis is truly an efficacious medicine, and that yes, I could look forward to enjoying a well-nourished and dignified pregnancy.

Not only did the cannabis save my son from not having a mother during the duration of my hyperemesis, it saved the life of my child within my womb. Every day, I am grateful for her bright and vivacious existence. Developmentally, she has proven to be very advanced for her age. She began walking at eight-and-a-half months (norm eleven to thirteen months), and she began expressing herself quite articulately at a year-and-a-half. Her teachers at her children center frequently comment on her maturity and the advancement of her motor, social, and cognitive abilities. I was told by one of her teachers that the university pediatricians who frequent the school to conduct research in child development were also highly impressed by her accelerated abilities. So for my situation, it is safe for me to conclude that my choice to use cannabis as a therapeutic "folk" remedy for my HG symptoms was a positive and beneficial decision with healthful and quite amazing results for my daughter.

And no, I am *not* a "drug addict" as the stigma dictates. As soon as my symptoms of HG passed, I no longer needed to use the cannabis. My Taiwanese medical obstetrician who helped deliver my daughter informed me that since ancient times the Chinese have used cannabis to treat HG, and the smoke that is inhaled does not go to the fetus, but rather directly to the brain of the mother to help counteract her nausea and stimulate her appetite. Studies also confirm that "only rela-

tively small amounts" of the psychoactive cannabinoid ingredient-delta-9-THC "actually cross the placenta barrier to the fetus" (Dreher 1997, p. 160). While medication in the form of pills is easily vomited by one who is susceptible to nausea, smoking/inhaling in this situation is actually a preferred route of administration. The HG mom more accurately and readily gauges the dosage of each treatment according to how she feels each time, unlike pills and suppositories that often leave one feeling "knocked-out" all day. As a result, I am in disbelief at how our government has kept such a valuable medicine from so many ailing women. If I had not experienced the cannabis myself, I would not have believed its truly effective and gentle therapeutic powers.

While I am not one to condone the use of illicit drugs during pregnancy, I strongly believe that in the case of women suffering from HG, an exception must be made in regards to the use of cannabis. In *Mothers and Illicit Drug Use: Transcending the Myths,* Susan Boyd (1999, p. 4) states:

> Critical researchers acknowledge that "crime" is a political construct . . . where selective criminalization takes place. In North America the most dangerous drugs are legal. Tobacco and alcohol are more lethal than the more benign drugs, such as marijuana, and both heroin and cocaine. The so-called dangers of illicit drugs are widely depicted by both government and the media. But the real dangers of legal drugs, including alcohol, tobacco, and pharmaceutical, are viewed differently.

She also emphasizes that of all the illicit drugs, cannabis is the most benign (Boyd 1999).

Personally, I did not appreciate my ability to use this herb until I learned of the extreme suffering experienced by other women with HG while at the hands of the well-intentioned medical community. How can one justify the extreme methods discussed previously as being less criminal than condoning women to use an herb that does not harm the fetus but simply offers the HG mother the chance to eat, drink, function normally, and experience the positive pregnancy she deserves?

Do I dare suggest that the medical hegemony and the pharmaceutical companies are suspect for not prioritizing the best interest of the mothers, but rather, their immense profit margins? For instance, while the cost for cannabis treatment, even at expensive street prices, might not exceed $400 for the entire duration of one's HG pregnancy, the medical cost of ondansetron, the anti-emetic pharmaceutical drug commonly used by HG women, is sometimes charged at $600 for each intravenous dose. Hypothetically, even if an HG sufferer took only three doses a day for sixteen weeks (the usual duration of HG, though some experience HG their entire pregnancy), the cost would be more than $200,000 (Grinspoon 1997, p. 42).

When I share my story with others, the reaction is either one of sincere enthusiasm and curiosity or apprehensive disapproval and skepticism. One HG woman, upon hearing of my self-remedy, instantly said, "*No, no, no . . . I wouldn't trust it*. What about the *side effects?* And besides, maybe your symptoms of HG were not as severe, and that's why you were okay without getting hospital treatment."

It is not surprising that my suffering was belittled and my cure denounced. Most view the use of illicit drugs, especially during pregnancy, to be deviant, threatening, and something to avoid at all costs (Boyd 1999). Murphy and Rosenbaum (1999, p. 1) state, "In modern society the use of illegal drugs during pregnancy is commonly defined as the antithesis of responsible behavior and good health. The two statuses, pregnant woman and drug user, simply do not go together."

This stigma, while serving its purposes to discourage careless behavior during pregnancy, is counterproductive in isolated situations that permit the medical use of cannabis by HG sufferers. In the United States and Canada, medical research on cannabis in relation to mothers and their offspring has produced reports that are fear-inducing and negative, often because the pregnant subjects involved use multiple drugs, come from low-income and disadvantaged situations, endure domestic violence, suffer from poor nutrition, and/or have pre-existing psychological disorders (Dreher 1997). However, propaganda and the media often conveniently exclude the latter details, misinforming the public into believing inaccurate and sensationalized perinatal risk factors caused by the side effects of the stigmatized "killer weed." These studies more accurately reveal the results of a dysfunctional lifestyle, and not the actual side effects of cannabis use. They marginalize the herb as a psychoactive, recreational drug rather than a therapeutic agent.

In the book chapter "Cannabis and Pregnancy," Melanie Dreher (1997) writes that much historical and cross-cultural evidence has been uncovered on the therapeutic uses of cannabis during pregnancy, labor, delivery, and nursing. In fact, archeological and written records substantiate that the plant was often used to treat female ailments, such as dysmenorrhea, ease labor, alleviate morning sickness/hyperemesis gravidarum, and/or facilitate childbirth in places such as: Ancient Egypt, Judea, and Assyria (Mathre 1997), ancient China (Grinspoon 1997; Mathre 1997, p. 36), historical Europe (Benet 1975), rural Southeast Asia, specifically Cambodia, Thailand, Laos, and Vietnam (Martin 1975), Jamaica (Dreher 1975), Africa (Du Toit 1980), and colonial and contemporary America (Grinspoon 1997; Mathre 1997; Wright 1862; www. folkmed.ucla.edu). Dreher's anthropological study reconfirms many of the historical and contemporary findings. Conducted in Jamaica amongst Rastafarians who highly esteem cannabis as a sacred herb and therapeutic agent for a wide spectrum of ailments, the researchers in the study were stunned to discover that babies whose mothers

used cannabis throughout their pregnancy (whether or not they had the symptoms of nausea and vomiting) were healthier, more advanced, more alert, and less irritable than infants whose mothers did not use cannabis. What the team revealed through time-consuming, labor-intensive research and observation, Jamaican women knew all along, claiming that (Dreher 1997, p. 164):

> smoking and drinking *ganja* [cannabis] was good for the mother and the baby because it relieved the nausea of pregnancy, increased appetite, gave them strength to work, helped them relax and sleep at night, and in general, relieved the "bad feeling" associated with pregnancy.

From personal experience with my own "cannabis baby," I can attest to the validity of these conclusions. Similar to the results of the study, my daughter is "healthier, more advanced, more alert, and less irritable" than other infants her age.

TWO WOMEN'S STORIES OF USING FOLK, ALTERNATIVE MEDICINE

In Winter 2000, when I discovered through various parenting and childbirth websites the pervasiveness of HG, I decided to post a short message in a midwifery Internet site, sharing with others that I had discovered a non-pharmaceutical, natural cure and that anyone interested could contact me at my E-mail address. I felt that unless I shared my experiential knowledge, I would be withholding valuable information from women who could otherwise benefit from this re-discovered ancient folk remedy. Due to its controversial and illicit nature, I purposely posted a message that was vague, suppressing the fact that I was referring to cannabis. Only when I received an electronic-mail query did I reveal to the person the actual name of the herb, along with an option to request more detailed information if they were still interested. Of over fifty people who wrote to me in the following months to learn more about the herbal medicine, two women followed through, deciding to use cannabis medicinally for their hyperemesis. They both had negative experiences with mainstream medical procedures and pharmaceutical drugs during their previous pregnancies and were determined to find alternatives. When they first corresponded with me they were not pregnant, but after months of researching further into the prospect of using cannabis they eventually felt secure enough to conceive, hoping that the herb would work as efficaciously for them as it did for me. Although I did not interview them in the traditional sense, insights into their personal lives and profiles slowly emerged through correspondence.

The first woman, "Gina," is an elementary school teacher living in Southern California. When Gina first E-mailed me, she wrote:

> I had HG with my sons, now aged 19 and 17, and I had my most severe HG with my last pregnancy, which ended in a fetal demise at 14 weeks. I want to try again very much for another child (this is my second marriage, and my husband has no children). But I am deathly afraid of the HG . . . I am so glad you are researching this disease. It is a crime that so many women have to suffer.

The second woman, "Didi," shared similar feelings. In her first correspondence, she wrote:

> I would love to hear about a natural cure [other] than [pharmaceutical] medicine. I just lost a baby at 5 months [when] I was on Reglan pump and IV Picc line. I started to feel better, then the baby just died with no reason. I lost another baby two years ago at 13 weeks. Any advice is welcomed . . . My husband does not want to try again because of my condition. I should tell you I do have a 7-year-old son. I was sick with him but not as sick as I get now. I think it is because I am older now too (32-years-old).

The challenges that Gina and Didi faced in considering cannabis as a therapeutic option were similar. The first obstacle was the lack of social and medical support that they felt in considering the use of a stigmatized therapy. Although open-minded, they still experienced feelings of fear and guilt, especially while using cannabis. For instance, although Gina repeatedly stated in many of her correspondences to me that she felt "very comfortable" with the thought of treating her HG with cannabis, her confidence level was soon undermined by others: women on the internet chastised her, her husband discouraged her from relying upon it as the sole medicine, and her obstetrician was "very curt and uninterested" even before she could share with him her newly discovered medical choice. Although Gina lives in California and could logistically use medical cannabis under the protection of the Compassionate Use Act of 1996, she decided that it was best that she kept her "secret remedy" to herself, stating that she was "afraid to say anything," but was "not afraid to do it" in the privacy of her own home.

Didi also had fears in contemplating the use of the herb. When she asked her obstetrician if he could help her research the medicinal benefits of cannabis for pregnant women, he told his nurse to tell Didi that he was "too busy" and that she should do the research on her own. She followed his instruction, investigated the topic, and sent him her findings on the use of cannabis as a viable treatment for HG; in response, he refused further discussion, and sent her "pamphlets on the dangers of drugs" without additional comment. The doctor's callousness and lack of understanding and support deeply angered Didi. She later confided her feelings: "You would think that after everything I went through [losing two chil-

dren due to HG], he would look into it harder with an open mind. This leads me to question . . . When I do find my next doctor [whether] to say nothing at all." Didi became more discouraged when she heard through her "sister's friend's aunt who is a nurse" that "doctors still check for drugs without your consent." In one of her E-mails, she asked me, "This is Michigan–is that possible? Will they send the social workers after me? Or is this a scare tactic?" Although I replied to her that by law, a woman has the right to not sign the consent form, she replied through E-mail with the proof of her findings:

> There was this one [woman's story posted on cannabisculture.com] that scared the SHIT out of me–by a woman named Aislinn who used cannabis throughout her pregnancy (recreationally) and they tested her baby for drugs [cannabis only]. Now they are taking her newborn away. What they said was she signed a consent form for treatment. They can test her for whatever they want. But who would think drugs? I am really scared now. I don't want to take any chances of losing my son and my new baby (whenever that happens).

A few weeks after this correspondence, Didi ceased relying on the internet as a source of communicating, opting to use the telephone for the purpose of privacy and legal safety. She reasoned that the few sites that discussed cannabis usage during pregnancy were "shut down" simultaneously and all too "coincidentally," as if the government was censoring data being exchanged over the internet and "making it harder for women" to openly exchange information. Whether this was a valid conclusion or an unfounded hypothesis I am not sure, but of certainty is the element of fear that continued to linger in Didi's consciousness.

According to researchers who have studied the properties of cannabinoids, two factors that are crucial to consider when a person uses a "psychoactive drug" such as cannabis are the "set and setting." Mathre explains in *Cannabis in Medical Practice* that "*set* refers to the mood and expectations of the user and *setting* refers to the environment in which the drug is used" (Mathre 1997, p. 175). Hence, if a person is already sensing "fear, guilt, and paranoia," these same feelings will become more exaggerated after the intake of cannabis, which can prevent the therapeutic properties from taking effect. Possibly, Gina and Didi's fear-laden set and setting took away from the women's abilities to allow the medicine to completely alleviate their symptoms. Gina stated in one of her correspondences:

> I started using [the herb] between weeks 5 and 6, when the symptoms started. It helps enormously! I still don't feel wonderful–I still don't have an appetite for food, I have to make myself eat, but at least it stays down,

> and I can keep my liquids up . . . I know the nutrition part is really gonna bring this thing together.

Although the cannabis actually helped her achieve the relief that no other pharmaceutical drug had offered, she confessed that she continued to feel "nervous" and "guilty." In order to hide the fact that she was using cannabis for her nausea, she also took Diclectin to explain her relief without exposing her "secret remedy" to her obstetrician. She explained: "Still taking the Diclectin. Doctor said he'll order as much as I need. But it is really the cannabis that is saving me, because some days I am too sick to swallow the pills, so I smoke about two hits, wait a while, then I am able to eat and drink a little." Therefore, even though cannabis provided the true relief, she took the Diclectin to prevent suspicion from her obstetrician. The cannabis she obtained simply did not do much for her. It made her sleep a lot, counteracted her nausea and vomiting only slightly, and made her feel "paranoid and afraid." Its unsatisfactory effects could be traced to a number of possibilities: (1) the particular strain of the cannabis, (2) her psychological and physiological state, the "set," and (3) her environmental situation, the "setting." For the first point, both Gina and I have concluded through sharing our experiences that strains of *Cannabis indica*, while more potent, were less effective for us than *Cannabis sativa* strains in counteracting the nausea and vomiting of HG. Indica seemed to render the patient more vulnerable to paranoia, while sativa alleviated nausea/vomiting without the residual feelings of "getting high." In response to the second and third points: the controversial and illicit nature of the drug, along with the government's unwillingness to conduct further research, make situations even more difficult for women who could truly benefit from comprehensive guidelines and medical endorsement.

Procuring the illicit herb proved to be a challenge for both women. Gina had an easier time in Southern California. Didi had more difficulty acquiring good product in Michigan. It was no surprise to me when she later told me that she was not getting much, if any, relief from her cannabis. By the time I committed the risky and illicit act of sending some higher quality sativa via the mail, it was already too late and she had turned to the hospitalized treatment of HG, where her doctor started her on an intravenous line to receive liquid nutrition and ondansetron to curb her nausea and vomiting.

For Gina, cannabis was effective enough to keep her out of the hospital. Through experimentation, she found she was able to "autotitrate" (Mathre 1997, p. 146) according to what her body demanded:

> I haven't been getting sick in the middle of the night, which is great, because I can get some sleep. The times I have felt sick, I just get up and take a hit, then I'm fine. Sometimes I have to take up to 6 hits a day, 2 in the early morning, 2 in the afternoon, and 2 at night. But usually, it is about 4 hits, 2

> in am, 2 in pm. I am no longer worried about it–because the alternatives are to be in the hospital again, or not go through with the pregnancy. The cannabis is really what is saving me–because I am able to eat and drink some, I can still work, although it is far from pleasant.

Unfortunately, in December 2000, I received the sad news that Gina miscarried as in her previous pregnancy. She stated: "The doctor said the fetus appeared to be about 13-14 weeks old, so I do not believe for a second that the cannabis or the Diclectin® caused the fetal demise. There's something else going on." She said that her obstetrician was going to follow up with different chromosome and blood tests so that she could see why her body was "rejecting the fetuses." In spite of the tragic ending, Gina wrote to me: "I want to thank you for your support. I still believe in the medicinal value of cannabis for hyperemesis." I mourned Gina's miscarriage not because I had lost a potential candidate to study the use of cannabis for HG, but because she had lost a much-wanted child, a heartbreaking process that many, many mothers with HG too often endure. Fortunately, Didi's baby was birthed in health and wellness.

CONCLUSION

In retrospect, I wonder if my home-based, underground, pilot study on HG and cannabis was more depressing than it was encouraging. While my findings revealed some promise, I am left feeling deeply frustrated by the social and legal impossibilities of engaging in a formal clinical study in present-day America. What grieves me most is the knowledge that women with HG continue to suffer with no medically (and legally) efficacious treatment when I am convinced that we already have the cure. The stories I have been privileged to know have left me with images that continue to haunt me: of Sofia with her thighs dwindled to the width of my thin arms, interchangeably crying and vomiting as she watches the food channel on television because she wants so much to be able to eat, but cannot in the devastation of hyperemesis; of Maria threatening suicide because she is given no choice but to be bound to endless machinery with tubes surgically inserted into her abdomen for feeding and drainage for the sake of keeping her baby alive; of Sarah, whose husband deserted her because she appeared like a "skeletal with a belly," looking like "death," smelling like "poison," and wanting to die every waking hour; of Gina, devastated with the discovery that she had lost a much wanted baby for the second time. These real-life tragedies bombard me with a dispirited, *"Why?"* Why do HG women continue to suffer, even amidst pharmaceutical and hospitalized treatments that can cost over hundreds of thousand of dollars of insurance money per pregnancy?

Why was I so blessed to have found a cure, one that cost no more than $90 for the entire duration of my HG? If it were not for the study of Jamaican pregnant

women who used cannabis safely with positive effects on their babies, and if it were not for my Taiwanese obstetrician who reassured me that birthing women in China have commonly used cannabis to alleviate their nausea and vomiting, and if it were not for Dr. Grinspoon at Harvard Medical School, with his extensive research on the medicinal properties of cannabis, who found credibility and value in my anecdote, I would definitely be filled with self-doubt in the face of surrounding fear, persecution, and paranoia. While I should simply let the issue pass, a part of me is unwilling to give up so easily, partially because cannabis is an important, but lost, part of my cultural heritage. Having experienced severe hyperemesis, I can empathize with all the women who also endure its debilitating effects. If one could imagine surviving the nausea and retching of food poisoning combined with vertigo and motion-sickness non-stop for four to nine months straight, night and day, than one could possibly begin fathoming the physical and psychological trauma of living with HG.

In summary, it is relevant to ask: What are the rites and rights of birth offered to a woman with hyperemesis within the realm of modern medicine? The rites are obvious: *the ritual of isolation*, when the woman is attached to tubes and machines in the hospital, sometimes for the entire nine month duration, torn from her community of family and friends; *the ritual of sacrifice,* when the woman's body, viewed as an "object" rather than a "subject," is poked and prodded, severed and bloodied as she is merely treated as the container who must somehow "produce" the baby, the "product" (Davis-Floyd 1992, pp. 160-161); *the ritual of denial,* when the woman's incessant and tenacious nausea and vomiting is downplayed as being "all in the head," or accused as a way for her to "vomit out her baby" or disguise her "bulimia" disorder; *the ritual of suffering*, when the woman is expected to withstand the tortures of highly gruesome medical procedures that involve the surgical cutting and ripping of flesh without anesthesia, bear the pangs of long term starvation, and endure the end result of a "chronically collapsed digestive system"; *the ritual of silence*, when the woman's voice is not heard, in spite of her cries for help, and her body is not acknowledged, in spite of its emaciation. And finally, within these rites is simply her right to give birth with much medical intervention but no real cure.

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The Consequences of Marijuana Use During Pregnancy: A Review of the Human Literature

Peter A. Fried

SUMMARY. In spite of marijuana being the most widely used illegal drug among women of reproductive age there is a relative paucity of literature dealing with this topic. Of the data available, particularly in offspring beyond three years of age, most is generated by two ongoing cohort studies with very different populations. Both have reported similar findings. Up to approximately 3 years of age there appears to be very little impact upon the offspring. Beyond that age, *in utero* cannabis exposure does not impact upon standardized derived IQ scores but is negatively associated with attentional behavior and visual analysis/hypothesis testing. These findings are hypothesized as prenatal marijuana exposure having a negative influence on aspects of executive function–a "top-down," multifaceted cognitive construct involved in organizing and integrating specific cognitive and output processes over a interval of time. The results and their interpretation are examined in terms of behavioral teratogenic effects (or lack of effects) during the various developmental stages of the offspring, the non-unitary

Peter A. Fried, PhD, is Professor of Psychology, Carleton University, Ottawa, Ontario, Canada K1S 5B6 (E-mail: peter_fried@carleton.ca).

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nature of executive function, cannabis receptors, and the consequences of chronic marijuana use in the non-pregnant population.

KEYWORDS. Prenatal marijuana exposure, pregnancy, executive function, prefrontal lobe, longitudinal studies, IQ, visual perception, attention

In the ongoing debate about the role of cannabis and health as well as the increased interest in amending laws pertaining to the legal status of marijuana there is one area that appears noteworthy for its lack of inclusion: the possible short- and long-term consequences on the offspring of women who use marijuana during pregnancy. Particularly as applied to the long-term cognitive and behavioral outcomes, the absence of this issue reflects, at least in part, the relatively sparse body of information available on this topic. Contributing to this paucity are a myriad of complex pragmatic, logistic and interpretative difficulties that are part and parcel of the longitudinal behavioral teratological research that is required to examine this question. These design issues have been the subject of a recent review (Fried 2002) and will not be reiterated in the present paper. In spite of the difficulties involved in the gathering of information, the indisputable fact that marijuana is the most commonly used illicit drug among women of reproductive age (Johnston et al. 1994; 1996) emphasizes the need for the gathering and dissemination of data from well controlled studies.

In NIDA's most recently completed National Pregnancy and Health Survey (1996), self-reported marijuana use during pregnancy was 2.9 percent which, incidentally, is approximately three times the frequency of cocaine/crack usage. Among high school seniors (those entering reproductive years), a December 2000 Monitoring the Future press release (*http://www.monitoringthefuture.org/data/00data/pr00t2.pdf*) reported that marijuana had been used by 22% of grade 12 students in the past 30 days. In our own work (the Ottawa Prenatal Prospective Study–OPPS), which will be described briefly later in this paper, among 120 predominantly middle-class 18-20 years olds, the rate of smoking a minimum of one joint in the past week, determined by self-report coupled with a urine analysis, was 34% and smoking at least that amount on a regular basis at some time during the past five years was 45% (unpublished data). In addition to the relatively extensive use of marijuana by both women who are pregnant and women of child-bearing age, among both heavy (e.g., Hurt et al. 1995) and social (e.g., Graham et al. 1992) maternal cocaine users, marijuana is frequently smoked. This adds additional importance to the determination of marijuana's possible pre-

natal impact for, in order to disentangle cocaine's potential effects, marijuana's role must be understood.

The purpose of the present paper, portions of which have recently appeared elsewhere (Fried 2001; Fried and Smith 2001; Fried 2002), is to objectively summarize the present state of knowledge pertaining to marijuana and pregnancy, an issue highly pertinent to the theme of this edition of the Journal.

Only two longitudinal cohort studies with very different sample characteristics have focused upon the possible consequences of prenatal marijuana in offspring beyond early school age. In our own work, the OPPS, the objective has been to examine the association between marijuana (and other socially used drugs) consumed during pregnancy and effects upon offspring in the areas of growth, cognitive development and behavior. This longitudinal work has been underway since 1978 with the sample consisting of low-risk, white, predominantly middle-class families. Details of the recruitment procedures, interview protocol and drug use ascertainment have been described elsewhere (Fried et al. 1980). In essence subjects within the sample, representative of the English-speaking Ottawa population, were interviewed once during each of the trimesters remaining in their pregnancy. Birth data have been collected from 682 women in the Ottawa area but, for pragmatic reasons, approximately 180 offspring were chosen to be followed beyond the neonatal period.

During each of the pregnancy interviews, information was collected concerning socio-demographic status, mother's health (both current and prior to the pregnancy), father's health history, previous obstetrical history, a 24-hour dietary recall, and past and present drug use with particular emphasis upon marijuana, cigarettes and alcohol. For the drug histories, information was gathered pertaining to the year before pregnancy and each trimester of pregnancy. During the pregnancy, neonatal, childhood and adolescent time frames for which data have been published, the OPPS has collected over 4000 variables. Further details describing the assessment procedures at various ages are presented throughout this paper.

The second longitudinal study that has reported on a number of outcomes of prenatal exposure to marijuana in children ranging in ages from infancy to early adolescence is the Maternal Health Practices and Child Development Study (MHPCD) based in Pittsburgh (Goldschmidt et al. 2000). This study was initiated in 1982 and has focused upon the consequences of prenatal use of marijuana, alcohol and cocaine. The subjects in this high-risk cohort are of low socioeconomic status and just over half are African-American. Growth, cognitive development, temperament and behavioral characteristics have been reported in offspring up to the age of 10 and the marijuana findings reported are those noted after controlling for other drug use.

In the discussion of the OPPS and MHPCD findings as well as other studies, unless otherwise stated, the results described have been reported in the original

articles as being statistically significant after controlling for potential confounding, mediating or moderating variables. In the present review, the use of the term significant refers to probability levels reported as > .05 whereas the term highly significant refers to probability levels of .01 or greater.

COURSE OF PREGNANCY

Over the centuries, in many parts of the world, marijuana has been anecdotally reported to hasten childbirth, with the drug increasing the frequency and intensity of contractions (Abel 1980). Contemporarily, Fried, Watkinson and Willan (1984) found a statistically significant reduction of approximately one week in the gestational age of infants born to mothers who used marijuana six or more times per week. A report (Greenland et al. 1982) that precipitate labor was significantly more frequent among women who reported using marijuana is consistent with the folk medicine and may be related to the shortened gestation noted in the OPPS sample. The approximate one week reduction in gestation length observed is of questionable clinical significance in and of itself. However, as the effect was dose related, the shortened gestation length may take on clinical significance if large amounts of the drug is consumed, if the Δ9-tetrahydrocannabinol levels are higher than those used in the early eighties, and/or if life-style habits include other risk factors such as alcohol. Some (Gibson et al. 1983; Hatch and Bracken 1986) but not all researchers (Tennes et al. 1985; Day et al. 1991) have reported an association between marijuana use during pregnancy and preterm delivery.

In the OPPS, no association with marijuana use and subjects' miscarriage rates, types of presentation at birth, Apgar status, and the frequency of neonatal complications or major physical abnormalities (Fried 1982; Fried et al. 1983) were found. No patterns of minor physical anomalies were noted among the offspring of marijuana users although two anomalies, true ocular hypertelorism and severe epicanthus, were observed only among children of heavy users of cannabis (O'Connell and Fried 1984). In general, researchers have not reported an association between prenatal marijuana use and morphologic abnormalities in offspring (e.g., Day et al. 1991) and, as reviewed elsewhere (Dalterio and Fried 1992; O'Connell and Fried 1984), the few reports of increased physical abnormalities may reflect a lack of control for confounding factors (e.g., prenatal exposure to alcohol) and/or the relative risk status of the women in the study.

The life-style and concomitant risk status are factors that appear to interplay with prenatal marijuana outcomes. For example, in the low-risk sample of the OPPS, no evidence of increased meconium staining was noted among the newborns of the heavy marijuana users (Fried et al. 1983). This observation contrasts with the first but not second of two reports by Greenland and associates (1982; 1983). One of the primary differences between the two Greenland studies was the

generally higher standard of living and health among the sample in the later (1983) report with these subjects being quite similar, demographically, to the OPPS sample. A study that manipulated non-marijuana factors and that utilized pregnant rats (Charlebois and Fried 1980) indirectly supports the critical role that life-style factors may have in interacting with the teratogenic effects of the drug. Briefly, different groups of pregnant rats were exposed to marijuana smoke while receiving diets varying in protein content. Compromised pregnancies were markedly potentiated when marijuana smoke was combined with a low-protein diet but, conversely, if marijuana smoke was coupled with a high-protein diet some risks associated with the cannabis exposure were attenuated.

GROWTH

The role of life-style interacting with marijuana's prenatal effect can be observed upon fetal growth (Fried et al. 1999). Most studies have not found marijuana to have a negative impact in this domain but, in some samples drawn from high-risk environments, a small but significant negative relationship between first trimester marijuana use and birth length (Day et al. 1991; Tennes et al. 1985) or birth weight and length (Zuckerman et al. 1989) have been reported. Intriguingly, in both the MHPCD and OPPS cohorts, prenatal marijuana use was associated with an increased weight: Day et al. (1994) found this association at birth between heavy third trimester use and birth weight in a minority, high risk sample, although it was not found with a combined marijuana and alcohol cohort (Day et al. 1994a) and Fried and O'Connell (1987) reported a positive relationship between marijuana use during each trimester and weight at 24 months in the low-risk, middle-class OPPS sample.

Of the few studies that have examined offspring beyond the newborn stage, no significant negative association with growth parameters was noted at 8 months (Day et al. 1992), 1 year (Fried et al. 1999; Tennes et al. 1985), 2 and 3 years (Fried and O'Connell 1987; Fried et al. 1999), 4 years (Fried et al. 1999), and 6 years (Day et al. 1994a; Fried et al. 1999). One growth parameter in the OPPS sample, a smaller head circumference, observed as a trend in all ages (birth, 1, 2, 3, 4 and 6 years) reached statistical significance among early adolescents (Fried et al. 1999) born to daily marijuana users but was not significant during mid-adolescence (Fried, James and Watkinson 2001). Maternal marijuana use was not associated with the timing of pubertal milestones in either adolescent males or females (Fried, James and Watkinson 2001).

NEUROBEHAVIORAL/COGNITIVE OUTCOMES IN NEWBORNS

The literature describing the neurobehavioral effects of prenatal marijuana use on the newborn, although provocative, is far from definitive. In the Ottawa sample, using the Brazelton Neonatal Assessment Scale (Brazelton, 1973), at less than one week of age, marijuana was associated with increased fine tremors typically accompanied by exaggerated and prolonged startles, both spontaneous and in response to mild stimuli (Fried et al. 1980; Fried 1982; Fried and Makin 1987). In the same sample, maternal marijuana use was associated with relatively similar observations in 9 and 30 day old infants (Fried et al. 1987). At 9 days, hand-to-mouth behaviour was associated with marijuana use during pregnancy. Many of the behaviours seen both in the newborn and at 9 and 30 days are consistent with, but milder in degree, than found among infants undergoing opioid withdrawal. Although these particular indicants of impairments in nervous system state regulation were not detected by some researchers (Richardson et al. 1995; Tennes et al. 1985), reports of altered autonomic arousal in other outcome measures have been reported. Neonates of maternal cannabis users have been noted as having an increased likelihood of exhibiting a high-pitched cry (Lester and Dreher 1989) and to spend less time in quiet sleep (Scher et al. 1988).

Habituation, which in infants is an indicator of nervous system functioning and integrity, was associated, in some studies, with prenatal marijuana exposure. In the OPPS sample, newborns of less than a week born to marijuana users have poorer habituation to visual, but not auditory, stimuli (Fried, 1982; Fried and Makin 1987). It is noteworthy that in a primate study (Golub et al. 1981), behaviour distinguishing marijuana offspring from controls was the failure to habituate to novel visual stimuli. At 9 and 30 days of age, no association in the OPPS sample was apparent between maternal marijuana use and visual outcome measures such as pupil dilation and nystagmus. Compared to the remainder of the sample, more marijuana babies demonstrated a lack of visual habituation but the increased incidence did not reach statistical significance (Fried et al. 1987). No negative relationship between infant behaviour and maternal marijuana use was found in three reports describing a Jamaican cohort (Hayes et al. 1988; Dreher, Nugent and Hudgins 1994; Dreher 1997), nor in two different American studies (Tennes et al. 1985; Richardson et al. 1989). However, the possible vulnerability of aspects of visual system functioning in the neonate is a theme that recurs both in the longer term evaluation of offspring of maternal marijuana users in the OPPS and MHPCD cohorts as well as in a polydrug study (Griffith et al. 1994). This recurrent pattern will be discussed later in this paper.

NEUROBEHAVIORAL/COGNITIVE OUTCOMES IN LATE INFANCY AND PRESCHOOLERS

Findings pertaining to the impact of prenatal marijuana exposure on offspring between the ages of 1 and 4 are quite limited but, in what is available, there is a degree of consistency that is intriguing. In the OPPS (Fried and Watkinson 1988), using the Bayley Scales of Infant Development (Bayley 1969), no association between marijuana use during pregnancy and infant mental or motor development was observed at 1 year of age. No relationship between Bayley outcomes and prenatal marijuana exposure has been reported by other workers (Astley and Little 1990; Tennes et al. 1985). In the high-risk MHPCD cohort, the use of 1 or more joints per day during the third trimester was associated with lowered mental scores on the Bayley at 9 months of age but no longer at 18 months (Richardson et al. 1995).

The failure to find an association between prenatal marijuana exposure and a variety of cognitive outcomes persisted in the OPPS sample until the offspring were 4 years of age. At 2, although there was a negative association with language comprehension, this relationship did not retain significance when the home environment was statistically controlled (Fried and Watkinson 1988). At 3 years of age, after controlling for confounding factors, prenatal marijuana exposure was not associated with language expression and comprehension or decreased cognitive scores (Fried and Watkinson 1990).

However, one year later, an association with prenatal marijuana exposure that remained significant after controlling for confounding factors, was observed. These four year old children in the OPPS, born to women who had used marijuana on a regular basis during pregnancy (more than 5 joints a week), scored significantly lower than the remainder of the sample on a number of verbal and memory outcome measures (Fried and Watkinson 1990) derived primarily from the McCarthy Scales of Children's Abilities (McCarthy 1972). These findings were similar to results from the MHPCD cohort when the children were 3 years of age (Day et al. 1994b) in that, among the offspring of women who had used marijuana on a daily basis, an impairment on the short-term memory, verbal and abstract/visual reasoning subscales of the Stanford-Binet Intelligence Test (Thorndike et al. 1986) was noted. In a study investigating the interaction between prenatal cocaine use and a number of drugs including marijuana in 3 year old offspring, maternal marijuana use of an unspecified amount was related to poorer performance on the abstract/visual reasoning subscale of the Stanford-Binet test (Griffith et al. 1994). In all three studies with these preschoolers there was no marijuana effect on the composite, intelligence scores. As will be emphasized below, this has important interpretative and theoretical consequences in evaluating the findings in school aged children prenatally exposed to marijuana.

Reports focusing upon the behavioral and cognitive outcomes in offspring beyond 36 months of age exposed prenatally to marijuana are limited to that of the OPPS and MHPCD. Within these two cohorts, as there was at younger ages, there is a considerable degree of concordance in the findings in the children beyond 3 years of age. Furthermore, in these longitudinal studies, as the offspring get older, the observations are consistent with and logically extend, in a number of ways, the outcomes reported at earlier stages of development. One sphere of functioning, which may be impacted by prenatal marijuana in the school-aged children, is within the behavioral/cognitive construct of executive function (EF). The hypothesis of a negative association between *in utero* marijuana exposure and facets of EF in older offspring has been developed elsewhere in detail (Fried 1998) and will be described briefly in the following sections of this paper.

EXECUTIVE FUNCTION (EF)

The nature of EF involves the interplay of subordinate cognitive operations and thus may be viewed as an overarching, "top-down" cognitive domain. EF involves the ability to organize and integrate specific cognitive and output processes over an interval of time (Denckla 1993). The mental control processes involved in carrying out such future oriented behaviors include cognitive flexibility in problem solving, sustained, focused attention, inhibition of prepotent responses, monitoring, evaluating and adjusting self-directed responses and working memory (the temporary storage of information while processing incoming data). EF therefore describes a multiple, non-unitary set of functions needed to successfully carry out effortful, non-routine, goal-oriented tasks (Fried 1998). In evaluating the adequacy of this higher-order, integrative mental control process in the offspring of marijuana users, competency in the underlying specific domains that are to be mentally manipulated and integrated must be ascertained (Fried and Smith 2001).

From both clinical and empirical research (e.g., Fuster 1989; Lezak 1995), EF has been shown to be primarily subserved by the prefrontal region of the brain although other structures such as the hippocampus and cerebellum are involved (e.g., Diamond 2000; Lezak 1995). Reflecting the prolonged developmental course of the prefrontal lobes, most EF behaviors are not apparent until the children approach or reach school age (Fried 1998; Levin et al. 1991; Welsh et al. 1991). It may be noteworthy that upon examining the distribution and concentration of cannabinoid receptors in the fetal, neonatal and adult human brain using autoradiographic procedures (Glass et al. 1997), binding sites were identified throughout the regions of the adult neocortex with the greatest density being in the middle gyrus of the frontal lobe, cingulate gyrus and temporal lobe. Although frontal cortex from either fetal or neonatal tissue was not available for analysis,

based on the material that was examined, the authors found that the receptor distribution was similar in the fetal and neonatal brain to the adult human brain except that the density of receptor binding was markedly higher in the developing brain. The conclusion reached by the authors was that one of the major cannabinoid receptor sites in the human brain is in that part of the forebrain associated with higher cognitive functions.

The role of the prefrontal lobes in human intelligence is complex. One must distinguish between intelligence as a capacity to engage in adaptive, goal directed behavior and intelligence as defined by performance on standard psychometric instruments (Fried 1998). Data derived from clinical studies in which injury to the prefrontal area has occurred (e.g., Damasio and Anderson 1993; Fuster 1989; Stuss 1992) suggest that the former but not the latter type of intelligence is vulnerable to prefrontal dysfunction. Underlying this disassociation, at least in part, is that traditional intelligence tests set up specific tasks and goals thus obscuring the assessment of such key aspects of EF as integration of domains of functioning, goal setting, planning and self-monitoring.

From the maturational perspective, the observations, summarized earlier, that no effects of the drug were observed in offspring beyond the neonatal period until the children were 3 (Day et al. 1994; Griffith 1994) or 4 years of age (Fried and Watkinson 1990) is consistent with the developmental course of executive functioning. Further, from a functional perspective in these studies of the preschoolers, the combination of an absence of a lowering of global IQ scores but a negative association with such subtests that assess memory and abstract/visual reasoning is also consistent with the hypothesis that *in utero* marijuana exposure impacts negatively on particular facets of EF.

NEUROBEHAVIORAL/COGNITIVE OUTCOMES IN SCHOOL-AGED CHILDREN

The data available on school-aged offspring born to women who used marijuana during pregnancy suggests an interesting, but certainly incomplete emerging picture. It is important to note that as of this writing, in neither the OPPS nor the MHCPD longitudinal studies has an analysis been completed to determine whether the children that were impacted at one stage of development were those that continued to be impacted at a later age.

At 5 and 6 years of age, no differences were noted in the prenatally marijuana exposed and non-exposed children in the OPPS when assessed with global tests of cognition and language (Fried et al. 1992). As mentioned above with respect to EF and intelligence, it is possible that the instruments used in this work (Fried et al. 1992) provide a general and broad description of cognitive abilities and may not be capable of identifying nuances in neurobehavior that discriminate between marijuana-exposed and non-marijuana-exposed children. In order to determine

whether this absence of an association was due to the limited assessment in the standardized intelligence test of such key aspects of EF as integration of domains of functioning, goal setting, planning and self-monitoring, two studies were undertaken to examine specific cognitive characteristics and strategies.

Both of these investigations involved the OPPS cohort when the subjects were between 9 and 12 years of age. In the first (Fried et al. 1998), a neuropsychological battery was administered that included tests that assessed various aspects of EF as well as tests designed to assess global intelligence. The second was a direct investigation of the possible influence of prenatal marijuana exposure on "top-down" visuoperception (Fried and Watkinson 2000).

In the report evaluating aspects of cognition (Fried et al. 1998) the assessment battery utilized included the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler 1991) with its 13 subtests and 6 additional tests designed to evaluate aspects of EF. Included among the latter were tests of sustained attention and inhibition of prepotent responses (Gordon and McClure 1984), a problem solving task that required visually deducing abstract categories while adjusting responses on the basis of negative and positive feedback (Reitan and Davison 1974), a timed, difficult tactile, self-monitoring task (Reitan and Davison 1974), a measure of oral fluency (Spreen and Strauss 1991), and a working memory task (Siegel and Ryan 1989).

The results of the WISC-III were intriguing. As with the data collected from the OPPS sample at earlier ages, there was no association between the Full Scale IQ and *in utero* marijuana exposure. Among the 13 WISC-III subtests only 2, the Block Design and Picture Completion subtests, significantly differentiated among levels of prenatal marijuana exposure suggesting that *in utero* marijuana affects particular rather than global aspects of intelligence.

In the Block Design subtest, the children are directed to assemble blocks to form a design identical to one presented in a picture. This non-verbal, concept formation task requires the ability of perceptual organization, spatial visualization and abstract conceptualization (Wechsler 1991). The Picture Completion subtest requires the subject to identify a missing portion of an incompletely drawn picture and tests the ability to differentiate essential from nonessential details (Wechsler 1991).

These two subtests of the WISC are multifaceted, involving basic visuo-spatial and visuo-motor abilities as well as higher order cognitive processes. The latter likely include planning, impulse control, visuo-construction and visuo-analysis. Importantly, the marijuana findings on the two WISC subtests persisted after statistically controlling for basic spatial and motor abilities thus supporting the interpretation that the impact of prenatal marijuana exposure on these WISC subtests is upon "higher-order" or "top-down" cognitive processes. Although not the subject of this paper, it deserves mentioning that these findings are in considerable contrast to those found among the offspring of cigarette

smokers. Both the IQ scores and virtually all of the WISC subtests (particularly those with a verbal aspect) served to discriminate across levels of prenatal cigarette exposure (Fried et al. 1998). This disassociation between the prenatal consequences of marijuana and cigarettes suggests quite strongly that the findings pertaining to marijuana are not some sort of artifact within the OPPS sample that, in a generic sense, would be found as a consequence to *in utero* exposure to any drug.

The finding that prenatal marijuana exposure impacted upon two subtests of the WISC-III that required complex visual analysis is consistent with observations noted in the two other reports mentioned earlier that focused upon prenatal marijuana exposure (Day et al. 1994; Griffith et al. 1994). At 3 years of age in both of those cohorts, the children of marijuana users were reported to have poorer abstract/visual reasoning skills based on the pre-schooler having to complete a formboard and replicate different block designs. This consistency of findings among different cohorts persisted at 10 years of age in the MHCPD cohort where prenatal marijuana use continued to be negatively associated with abstract/visual reasoning (Richardson and Day, 1997). At that age, this cognitive domain was assessed by performance on a block design task, a progressive matrices task and the ability to copy geometric shapes. As described in the "Neurobehavioral/Cognitive Outcomes in Newborns" portion earlier in this paper, it may be noteworthy, from a longitudinal perspective, that when the children in the OPPS were less than a week old, prenatal marijuana exposure was associated with poorer visual habituation (Fried 1982; Fried and Makin 1987).

Among the 9 to 12 year olds in the OPPS cohort (Fried et al. 1998), the results of the non-WISC outcome measures, which assessed aspects of EF, were consistent with and extend the observations for the marijuana groups gleaned from the WISC tasks. Of the two non-WISC-III tests that maximally discriminated among the marijuana groups was one that required the application of visual deduction to a problem solving task and the other was an assessment of impulsivity. Thus, of the six tests thought to assess aspects of EF, the two that were found to be associated with marijuana involve impulse control, visual analysis and hypothesis testing. This is consistent with the WISC results as the two subtests in that battery associated with prenatal marijuana use–Block Design and Picture Completion–require visual analysis and hypothesis testing.

This combination of visual analysis and impulsivity, but not other aspects of EF being vulnerable to prenatal marijuana, has been interpreted (Fried 1998, Fried and Smith 2001) as being consistent with conceptualizing EF as a non-unitary process. Developmental research not involving prenatal exposure to drugs and utilizing a factor analytic approach examining EF in children at different ages (Welsh et al. 1991) provides an important avenue of support for the marijuana findings from two perspectives. It both reinforces the general notion that successful executive functioning is a multifaceted process and also yielded find-

ings that are consistent with the specific facets of EF that appear impacted by prenatal marijuana exposure (visual analysis/hypothesis testing and impulsivity). Welsh et al. (1991), using an extensive battery of tests with a normative sample, identified three independent factors in the developmental course of EF reflecting planning, verbal fluency, and hypothesis testing while controlling prepotent responding. The latter was derived from a convergence of cognitive processes based on visual hypothesis testing and impulse control. These components contributing to this factor labeled "Hypothesis Testing and Impulse Control" are strikingly similar to those neurobehavioral outcomes negatively associated with prenatal marijuana exposure in the 9 to 12 year old OPPS subjects (Fried et al. 1988). On the other hand, the other two factors which Welsh et al. (1991) labeled as a "Fluid and Speeded Response" (including a verbal fluency and a tactile performance task) and "Planning" (including a working memory and a tactile task) were not found to be associated with maternal marijuana use.

In terms of the developmental time course of the "Hypothesis Testing and Impulse Control" factor, competence is achieved at around 10 years of age (Welsh et al. 1991). This is consistent with the observation that marijuana's negative effect in this dimension of EF manifested itself in the 9-12 year olds.

In another report based on the 9-12-year-old OPPS subjects, persuasive evidence was obtained for the notion that prenatal marijuana may impact upon "top-down" neurocognitive functioning (Fried and Watkinson 2000), a major interpretative cornerstone of EF. In this study, visuoperceptual tasks ranging from those that required basic capabilities to those that required considerable integration and cognitive manipulation were utilized. Further, in order to ascertain whether any change in visuoperceptual functioning may in fact be due to demands upon nonvisual facets such as attentional, memory and/or motor components, tasks were included to assess and control for these underlying behaviors.

The consequences of prenatal marijuana use on the performance of visuoperceptual tasks varied, depending upon the nature of the demands of the tests (Fried and Watkinson 2000). No association was noted between maternal marijuana use and those tasks that required basic, fixed, functional visuoperceptual abilities with little or no analytical or integrative skills. Where *in utero* marijuana exposure did have a negative impact was on tasks that required the application of these basic visuoperceptual skills to problems involving planning, integration, analysis and synthesis. This negative association remained after statistically taking into consideration prenatal confounds plus both basic visuoperceptual abilities and the non-perceptual variables described above. Interestingly, once again the findings pertaining to prenatal marijuana exposure were disassociated from maternal use of cigarettes during pregnancy. In contrast to the marijuana findings, prenatal cigarette smoking was negatively associated with both the fundamental capabilities and the application of those basic "building blocks" to the resolution of complex, visual tests–a "bottom-up" impact.

The results of this study, linking *in utero* marijuana exposure to a poorer performance on complex visuoperceptual tasks were interpreted as being consistent with earlier theorizing that prenatal marijuana exposure impacts negatively upon certain facets of EF and by association reflecting aspects of altered prefrontal activity (Fried and Watkinson 2000). The clinical literature describing individuals with damage to this neuroanatomical region is consistent with the proposed marijuana hypothesis linking prenatal exposure with an impact upon the prefrontal area. Patients with injury to this area of the brain are not impaired on basic visuoperceptual tasks but are markedly impacted on tests requiring visuoperceptual planning and integration (Luria 1973; Stuss 1992).

A further line of evidence suggesting a link between prenatal marijuana exposure and aspects of EF can be derived from studies that have focused upon attention–a complex, multidimensional behavior (Denckla 1996; Barkely 1996; Mirskey 1996) with attributes that have considerable commonality with aspects of EF (Barkely 1997). This overlap includes the ability to withhold prepotent but unsuited response tendencies, the capacity to screen out distracting or irrelevant stimuli while focusing on the task at hand, and the faculty of both flexibility and sustainability of focus when appropriate.

The OPPS and MHCPD cohorts have been used at various ages with a number of outcome measures to investigate this domain of functioning. Although different aspects of attention appeared to be impacted, prenatal marijuana use was associated with a negative effect upon attentional processes in both cohorts. Children in the two studies were given a Continuous Performance Task (CPT) (Greenberg and Kindschi 1996).

Both the OPPS (Fried et al. 1992) and MHCPD (Leech et al. 1999) offspring were assessed in this domain at age 6. In the OPPS offspring, prenatal marijuana use was significantly predictive, in a dose response fashion, of increased inattentiveness. In the children born to women who had used more than 5 joints of marijuana per week during pregnancy, inattentiveness increased as the CPT progressed, suggesting that among these more heavily exposed children sustained attention may be particularly vulnerable.

Among the 6 year olds in the MHPCD cohort (Leech et al. 1999), prenatal marijuana exposure was also found to impact upon attentional processes in terms of increased impulsivity. The authors speculated that prenatal marijuana exposure may slow processing speed and that the deficit would become more pronounced over a longer task and if time pressure demands were increased. The CPT results were interpreted by Leech et al. (1999) to be consistent with Fried's (Fried 1996; Fried et al. 1998) speculation that prenatal marijuana exposure impacts upon aspects of EF.

Facets of attention have been the focus of a recent report of the 13 to 16 year olds participating in the OPPS (Fried and Watkinson 2001). The assessment battery that was used in this study permitted the investigation of a number of compo-

nents of attention which were similar to those described in a multifactorial model of attention developed by Mirsky (1996). Five different elements of attention were identified by factor analytical procedures in Mirsky's model. These included the ability to focus, shift, and maintain attention, consistency of attentional effort over time ("stability") and a process that is conceptually very similar to working memory (Halperin 1996). Among the adolescents in the OPPS study, prenatal marijuana exposure was significantly related with that element of attention described as "stability." Subjects who had been exposed more than 5 times per week *in utero* manifested CPT reaction times that became less consistent as the test proceeded.

The negative impact of prenatal marijuana exposure upon attention noted in the adolescents (Fried and Watkinson 2001) is similar to the findings in the same cohort on a CPT at 6 years of age (Fried et al. 1992). The wide range of ages over which this relationship has been found is consistent with the developmental course of sustained attention which, unlike some other elements of attention, continues to develop throughout childhood and adolescence (McKay et al. 1994).

In the OPPS work when the children were 6 years of age (Fried et al. 1992), in addition to the CPT assessment, the mothers were asked to rate their offspring using a behavioral symptom checklist (Conners 1989). Consistent with the findings on the experimental task, the children exposed prenatally to marijuana were rated by the parent as more impulsive and hyperactive. Paralleling the OPPS observations, a recent report of the MHPCD cohort at 10 years of age (Goldschmidt et al. 2000) noted an association between prenatal marijuana exposure in the first and third trimester and increased parental reports of hyperactivity, inattention and impulsivity.

In this MHPCD study, based on both maternal ratings of child behavior and teachers' reports, an association between increased levels of delinquency and externalizing behavior associated with prenatal marijuana exposure was observed. Using a path analysis, poor attentional skills were interpreted as mediating the association between the mothers' report of delinquency and prenatal marijuana use. This relationship between prenatal marijuana exposure and the behavioral problems in the offspring is similar to an earlier trend noted in the OPPS cohort when the children were between 9 and 12 years of age (O'Connell and Fried 1991). Mothers who had used marijuana regularly during pregnancy rated their children as having a higher rate of conduct disorders but this difference did not retain significance after extraneous variables were controlled.

OVERALL CONCLUSIONS

Although predicated upon a limited body of literature, a suggestive, relatively consistent albeit nascent theoretical picture may be derived. The apparent effects

of prenatal marijuana exposure upon offspring are subtle. The emergent picture is that such exposure *in utero* may impact upon particular aspects of a complex higher-order cognitive process termed executive function. Although it is not possible to control all of the host of complex factors that possibly influence the outcomes of interest (Fried and Smith 2000; Fried 2002), the major studies cited have considered and have attempted to take into statistical account such potential confounders and moderating variables as other drug use, parenting socioeconomic status and the home environment. In the longitudinal OPPS and MHPCD studies, in spite of the marked difference in their racial and socioeconomic backgrounds, a considerable degree of similarity in findings is evident lending both validity and reliability to the findings.

The observations and interpretations of the data reviewed in this paper can be synthesized and summarized as follows. After the moderating effects of other risk factors are taken into account, the course of pregnancy, fetal and postnatal growth, and behavior during the neonatal and toddler stages appears relatively unaffected by prenatal marijuana exposure. However, starting at approximately 3 years of age, there are converging findings from a number of researchers implicating that such exposure negatively affect facets of EF, a multifaceted, higher-order cognitive process mediated primarily by the prefrontal cortex. In particular, aspects of EF which appear impacted in the older offspring by maternal marijuana use are in two domains: (1) problem solving tasks that require complex visuoperceptual integration and (2) attention/impulsivity. Consistent with this proposed association is the developmental literature which has identified, via factor analysis, that these two cognitive processes follow a single maturational course.

Although there is a degree of consistency in the extant literature relating prenatal marijuana exposure and the consequences in offspring, the paucity of studies from which the data have been derived (particularly in children older than 3) coupled with the issues raised in the opening paragraphs combine to emphasize the continued need for well-controlled investigations in this topic.

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Cannabis and Harm Reduction: A Nursing Perspective

Mary Lynn Mathre

SUMMARY. The goal of nursing care is to promote health and reduce harm caused by injury, disease, or poor self-care. Harm reduction is a public health model, which is gaining popularity as an effective modality to help persons reduce the negative consequences associated with their drug use. The harm reduction model blends well with the core principles of nursing. When viewed from a nursing perspective, cannabis could be an effective harm reduction agent based on its high benefit-low risk ratio when compared to other standard medications/drugs. As a medicine, cannabis has demonstrated a high therapeutic potential with relatively few side effects or adverse reactions. As a social/recreational drug, cannabis has a wide margin of safety with relatively few risks. The greatest risks from cannabis use are the legal consequences, which are the result of the cannabis prohibition rather than the drug itself. The therapeutic relationship between individuals and their health care providers is severely compromised by the cannabis prohibition. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress. com> 2002 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Cannabis, medical marijuana, harm reduction, nursing, social drug use, recreational drug use, adolescent drug use, cannabis prohibition, marijuana prohibition

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Mary Lynn Mathre, RN, MSN, CARN, is Addictions Consult Nurse, University of Virginia Health System, Charlottesville, VA, and President and Cofounder of Patients Out of Time, 1472 Fish Pond Road, Howardsville, VA 24562 (E-mail: ML@medicalcannabis.com).

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INTRODUCTION

Nursing is the art and science of caring. Since 1999 when nurses were included in the Gallup "Honesty and Ethics" poll, nurses have been rated as one of the most trusted professional groups by the American public (http://www. gallup.com/poll/releases/pro011205.asp). What is it about nurses that the public is willing to trust? Could it be that nurses often see people in their most vulnerable states and during that time treat them with respect and provide a safe environment to nurture them back to a more independent self-caring state? Nursing is much more than simply caring and providing comfort; it involves the art of knowing how to give the right kind of care and comfort to facilitate the healing process, and this knowledge is based in science. The goal of nursing care is to promote health and reduce the harm caused by injury, disease, or poor self-care.

Nurses are the largest group of health care professionals, and are keenly aware of the potential risks related to medications. While pharmacists dispense medications and physicians prescribe medications, nurses administer them to countless numbers of patients and monitor the effects of the medications. Nurses are in a key position to see not only the beneficial effects of a particular medication, but also the side effects or adverse reactions that can accompany medications even when used as recommended. Safe administration of medication is a critical skill all nurses must master because any error could cost a patient added suffering, organ damage, or could result in death.

Harm reduction is a public health approach to human behaviors, which involves helping persons learn to make better personal choices to minimize the potential risks associated with their behavior. Examples of harm reduction practices include using condoms properly during intercourse to avoid STDs, wearing a seatbelt when traveling in a motor vehicle, or using a helmet when riding a motorcycle. Today, harm reduction is gaining popularity as a more effective and realistic modality for helping persons who use drugs to reduce negative consequences associated with their drug use. Such harm reduction strategies include needle exchange programs for intravenous drug users to prevent blood-borne infections, use of a designated driver for persons consuming alcohol away from home, overdose prevention education, and offering a variety of drug treatment options (www.harmreduction.org).

Harm reduction is based on the premise that people are responsible for their behavior, that they make personal choices that affect their health and well-being, and that they can make safer and better decisions if given useful and honest information. The harm reduction approach accepts the fact that individuals will use drugs for various reasons and offers to help them "where they're at." In contrast, the War on Drugs is based on the premise that certain drugs are "bad" and that the government has the paternal right and duty to prohibit the use of these drugs. This "zero tolerance" or "just say no" approach condemns the use of certain drugs and

punishes those who use them. Acceptance comes after transgressors admit their wrongful ways and adhere to the abstinence option.

The underlying flaw in the war on drugs is the belief that some drugs are inherently bad and therefore deserve to be prohibited for the greater good of society. A drug is not simply good or bad, right or wrong, but rather the manner of use of a drug by an individual may be helpful or harmful. The harm reduction approach is based on science and the respect of others, while the war on drugs is based on moralistic ideology and the control of others. Drug use will always have the potential of causing sequelae. Harm reduction strives to minimize the harmful effects from drug use, while the drug prohibition creates more harmful effects from drug use.

Cannabis is an herbal agent that has been used as a medicine, a recreational drug, as well as a source of food and fiber. It is environmentally friendly, essentially non-toxic, yet currently forbidden by our federal government. US citizens are prohibited from growing this plant or possessing any of its leaves, seeds, stems or flowers. Physicians are forbidden to prescribe it for medical use. When the cannabis plant is examined in a scientific and logical manner, its therapeutic value becomes apparent. From a nursing perspective cannabis could be a useful harm reduction tool, yet the laws prohibiting its use present contrived risks that can cause more harm than the drug itself.

This article will examine cannabis as a harm reduction agent from a nursing perspective. Cannabis as medicine is not a magic bullet that will work for everyone, and is not without potential risks. Cannabis as a recreational drug is not enjoyable for everyone and is not harmless, but when put in the broader perspective and compared to standard medicines or common recreational drugs, cannabis offers greater benefit with fewer relative risks.

CANNABIS WAS A MEDICINE IN THE US

Prior to the prohibition of marijuana, cannabis products were widely used by physicians. By the 1930s there were 23 pharmaceutical companies producing cannabis preparations. In 1937, the passage of the Marihuana Tax Act marked the beginning of the cannabis prohibition. The head of the Federal Bureau of Narcotics (now the Drug Enforcement Administration or DEA), Harry Anslinger, led this legislative effort using exaggerations and lies (Bonnie and Whitebread 1974). During the congressional hearings the American Medical Association (AMA) opposed the Act and supported cannabis as a therapeutic agent. The lawmakers won and the AMA has since given up the fight.

The Controlled Substances Act of 1970 furthered the cannabis prohibition when it called for a system to classify psychoactive drugs according to their risk potential. Five Schedules were created, with Schedule I being the most restrictive

category. Under the Act, cannabis was initially placed in Schedule I, but Congress called for a National Commission on Marihuana and Drug Abuse to determine whether or not that placement was appropriate. President Nixon appointed most of the commissioners including the former Republican Governor of Pennsylvania, Raymond Shafer, as the chairman. The "Shafer Commission" completed their study in 1972, and it remains the most comprehensive review of marijuana ever conducted by the federal government. In the end, the Shafer Commission concluded that cannabis did not belong in Schedule I and stated (National Commission on Marihuana and Drug Abuse 1972, p. 130), "Marihuana's relative potential for harm to the vast majority of individual users and its actual impact on society does not justify a social policy designed to seek out and firmly punish those who use it." The recommendations were ignored and cannabis remained in Schedule I, a forbidden drug.

Now, thirty years later, the infamous Nixon tapes of Oval Office conversations from 1971 to 1972 have been declassified and made available to the public (transcripts available at www.csdp.org). It is clear that Nixon used his political power to influence the outcome of the Shafer Commission, and when that didn't work he simply dismissed their recommendations and launched the war on drugs. Curiously, at the same time, the Bain Commission in The Netherlands (with a similar mission) issued its report with similar findings. The government of The Netherlands acted on the recommendations of the Bain Commission, and today the Dutch have half of the per capita cannabis use as the U.S., with far fewer drug-related problems at much lower drug enforcement costs (Zeese 2002).

CANNABIS AS A HARM REDUCTION MEDICINE

Compared to standard medications, cannabis has a remarkably wide margin of safety. In 1988, after a lengthy legal battle to reschedule cannabis, the DEA Administrative Law Judge, Francis Young, ruled that marijuana should be assigned to Schedule II and thus available for physicians to prescribe. In his summary he noted that (p. 57), "Marijuana in its natural form is one of the safest therapeutically active substances known to man." Throughout the centuries of its use, there has never been a death from cannabis (Abel 1980). In contrast, there are more than 32,000 deaths per year associated with prescription medications in hospitalized patients (Lazarou, Pomeranz and Corey 1998). All opioids carry the risk of overdose. Even over-the-counter (OTC) medications can be lethal. There are approximately 120 annual deaths from aspirin.

Cannabis has been studied extensively in regard to determining its health risks. General McCaffrey called upon the Institute of Medicine (IOM) to study the therapeutic value of marijuana in 1997. In March of 1999 the IOM released its 18-month study, which concluded that cannabis does have therapeutic value and

is safe for medical use (Joy, Watson and Benson 1999). Concern was noted about the potential risks related to smoking medicine, but the study concluded that for patients suffering from cancer or AIDS, the potential pulmonary risks were minimal when compared to the benefits. The study also noted that while more research is warranted, cannabis is safe enough for physicians to conduct N-of-1 studies on their patients who they believe could benefit from cannabis if other medications are not effective.

The IOM report put health risks associated with cannabis in perspective noting (p. 5), ". . . except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications." A recent study of the chronic effects of cannabis on four of the seven federally provided medical marijuana patients showed minor bronchitis in 2 of the patients (Russo et al. 2002). These patients smoked from 5 to 10 low-grade (2% to 4% THC content) cannabis cigarettes on a daily basis for 10 to 20 years. No other attributable long-term problems were noted, but rather a reduction in their use of other medications and a feeling of well-being was experienced by the patients.

While smoking cannabis may cause lung damage after chronic use, there are various actions that can be taken to reduce the harm from smoking. Patients can smoke less if using a high potency product (THC content greater than 10%) and can easily adjust the dosage by decreasing the number of inhalations. Also, when smoking cannabis, patients should limit their breath holding to less than ten seconds to avoid lung damage (Tashkin 2001). Vaporizers are being developed that heat the plant material to the point of vaporization without combustion, thus avoiding smoke inhalation (Gieringer 2001, Whittle, Guy and Robson 2001). Finally patients may use cannabis in alternative delivery forms such as pills, sublingual spray, eye drops, suppository, dermal patch, or salve, thereby eliminating pulmonary risks.

The federal government claims that cannabis is harmful to the immune system. When reviewing the published animal studies that reported harm to the immune system the reader should note that most of the researchers used delta-9-tetrahydrocannabinol (THC) rather than natural cannabis and that extremely high doses were used. A review of the active ingredients in cannabis suggests that some of these constituents act synergistically to enhance the beneficial effects of THC, while others may mitigate the harmful side effects of THC including possible immunosuppression (McPartland and Russo 2001). Given the thousands of immuno-compromised patients who have used cannabis there have been no reports of direct damage to the immune system from cannabis except when the patient has used a contaminated supply. Many AIDS patients who, by virtue of their disease have a severely compromised immune system, do not show any decline in their health status related to cannabis. In fact, a recent study of cannabis use by AIDS patients showed that cannabis did not interfere with protease

inhibitors and helped increase weight gain for a significant number of patients (Abrams et al. 2000).

Another cannabis risk has been an allegation that it causes brain damage. Although the federal government continues to use this scare tactic, modern research has not confirmed such findings. A Johns Hopkins study examined cannabis' effects on cognition on 1318 subjects over a 15-year period (Lyketsos et al. 1999). The researchers found no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis. They concluded that the results provided strong evidence of the absence of long-term residual effects of cannabis use on cognition.

Perhaps the most illogical argument the federal government uses to prohibit the therapeutic use of cannabis is that to allow its medical use would "send the wrong message to our youth." General Barry McCaffrey openly fought the growing popular opinion and scientific findings that cannabis has medical value. In response to the passage of state initiatives allowing the medical use of marijuana, McCaffrey dismissed its therapeutic value and declared that state laws allowing medical use of cannabis would increase the rate of drug use among teenagers. He stated, "While we are trying to educate American adolescents that psychoactive drugs are bad, now we have this apparent message that says 'No they're medicine. They're good for you'" (Substance Abuse Report 1996). That is nonsense. Teenagers don't think, "Insulin is medicine. It must be good for me." A persistent message that parents and health care professionals should demonstrate and reinforce with children and teenagers is that medicine is for sick people and that all medicine should be used with caution based upon an awareness of the risks and benefits.

Since nurses are advocates and health educators for patients, families, and communities, they have a key role in helping others learn to use medications safely. With more than 400,000 medication preparations available in the U.S. it is unlikely that any person can know everything about these medications. However, the user can reduce harm from medications by following some general guidelines designed to ensure that the risks are minimized. Mothers Against Misuse and Abuse (MAMA) has developed medication guidelines that persons may follow when using any OTC, prescribed medication, or recreational drug. The premise for these guidelines is that no medication is completely risk-free, but harm can be minimized if the user has appropriate information to make an informed decision. MAMA seeks opportunities to teach these guidelines to parents to help them set a good example for their children when it comes to the use of medications or recreational drugs (www. mamas.org). This includes essential information that nurses include in their patient education, such as the name of the medication, desired effect, possible side effects or adverse reactions, proper dosage and route of administration, risk of tolerance, dependence or drug interactions.

Pain is the most frequent symptom for patients seeking medical care. Cannabis analgesia provides a good example of its potential as a harm reduction medication. Innumerable chronic pain patients have found it difficult to find a balance between managing their pain and being able to function in daily life. Opiates are frequently used for management of severe pain, however they sometimes leave the patient feeling "drugged" and come with the risk of overdose and side effects such as constipation, nausea and vomiting. Increasingly, patients are acting on the advice of others and are trying cannabis as an analgesic.

Per numerous reports (Mathre 1985, Corral, Black and Dalotto 2002, Russo et al. 2002, Rosenblum and Wenner, 2002), the introduction of cannabis into pain management regimens has been very helpful. Most patients report a significant reduction in the use of opioids or need them on occasion for acute exacerbations; this reduction in the use of opioids lessens the risk for physical dependence. Cannabis is an effective antiemetic, and is not constipating. In summary, many chronic pain patients who use cannabis report that they feel better, experience fewer untoward side effects, are able to reduce their use of opioids and other medications, and are thereby able to eliminate additional side effects that may accompany those medications as well as the added risks from drug interactions.

Margo McCaffery (1968) has taught us that pain "is whatever the experiencing person says it is, existing whenever he says it does." Pain is a subjective experience and patient feedback is essential to effective pain management. Current national guidelines for pain management endorse McCaffery's standard (Jacox et al. 1994). Given patients' reports of pain control with cannabis and its relative safety, nurses recognize that cannabis should be an option for patients. To date 11 state nurses associations (AK, CA, CO, HI, MS, NJ, NM, NY, NC, VA, and WI) have passed formal resolutions supporting patient access to this medicine (www.medicalcannabis.com). In addition, the American Nurses Association's Congress on Nursing Practice issued a statement in 1996 calling for the education of all RNs on evidence-based therapeutic indications for cannabis.

CANNABIS AS A SOCIAL/RECREATIONAL DRUG

While the federal government may be waging a war on certain drugs, it is clear to onlookers that America is a drug using society. Americans are constantly bombarded with advertisements for drugs that can take care of any of life's problems. We have pills to help us sleep, to help us stay awake, to help us calm down, to help us feel better, to take away our pain, to regulate our bowels, and on and on. We tend to call these drugs, *medications*, and that identifies them as "good" drugs. Americans don't even consider caffeine as a drug, but for many a cup of coffee in the morning is a must to start their day. Caffeinated drinks are even marketed to our youth with such lines as: "Do the Dew"–as though kids need any

more energy. (For children with too much energy, we simply drug them with a "medication" such as Ritalin®.) We also have regulated drugs that are acceptable for adult usage. Alcohol can be used for enjoyment: "This Bud's for you." The tobacco industry is struggling with the mandated health warnings and their advertisement ploys. "Smoking may cause lung cancer" versus "You've come a long way baby" or the "Joe Camel" character.

Psychoactive drug use has and will be a part of our society. In the American culture, drug experimentation among adolescents is considered normative behavior (Newcomb and Bentler 1988, Shedler and Block 1990). Adolescence is a time of transition, when young people are trying to determine their identity. Testing limits are part of their developmental process and the "forbidden" drugs are for many a temptation too great to resist. A longitudinal study investigated the psychological characteristics and drug use patterns in children studied from age 3 to 18 (Shedler and Block 1990). Those adolescents who experimented with drugs (primarily cannabis) were the "best-adjusted" compared to abstainers and frequent users.

These children were tested prior to the initiation of drug use and there were notable antecedent personality differences. The frequent users were found to be relatively maladjusted as children, unable to form good relationships, insecure and showed signs of emotional distress. The abstainers were relatively over controlled, timid, fearful, and morose. Authors described (p. 617), ". . . the picture of the frequent user that emerges is one of a troubled adolescent, an adolescent who is interpersonally alienated, emotionally withdrawn, and manifestly unhappy, and who expresses his or her maladjustment through uncontrolled, overtly antisocial behavior." In contrast, they noted (p. 618), ". . . the picture of the abstainer that emerges is of a relatively tense, overcontrolled, emotionally constricted individual who is somewhat socially isolated and lacking in interpersonal skills." The experimenters were found to be psychologically healthy, sociable, and reasonably inquisitive individuals. Twenty years earlier Hogan et al. (1970) compared marijuana users with non-users in a college population. They found that users (p. 63) "are more socially skilled, have a broader range of interests, are more adventuresome, and more concerned with the feelings of others." Nonusers were found to be (p. 61) "too deferential to external authority, narrow in their interests, and overcontrolled."

Shedler and Block (1990) also examined the quality of parenting the children received through direct observations of mother-child interactions when the children were 5 years old. Compared to the mothers of the experimenters, the mothers of the frequent users and abstainers (p. 624) "were perceived to be cold, critical, pressuring, and unresponsive to their children's needs." They found no noteworthy findings involving the fathers of frequent users. However, when compared to the fathers of experimenters, the fathers of abstainers were seen (p.

625) "as relatively unresponsive to their children's needs and as authoritarian, autocratic, and domineering."

The researchers caution readers not to misinterpret their findings as an encouragement for adolescents to use drugs. The findings do indicate that problem drug use is a symptom, not a cause of personal and social maladjustment. It is also helpful to understand that experimentation with certain behaviors can be expected with healthy adolescents. When it comes to the potential risks of drug experimentation, cannabis is a relatively safer drug choice.

The federal government has historically used the *stepping stone* hypothesis and *gateway drug* hypothesis as valid reasons for the marijuana prohibition. The stepping stone hypothesis presumes that there are pharmacological properties in cannabis that lead the user to progress to other drugs, while the gateway theory presumes that as an illicit drug cannabis serves as an entry to access other illicit drugs. The premise of both theories is that cannabis use leads to harder, more dangerous drug *abuse*. There is no question that cocaine, methamphetamine, heroin or other hard drug users may have used cannabis in their earlier stages of drug use, but there has never been a causal relationship established. In fact, most drug users begin with alcohol and nicotine, usually when they are too young to do so legally. The Shafer Commission noted (p. 88), "No verification is found of a causal relationship between marihuana use and subsequent heroin use." The IOM report found that (Joy, Watson and Benson 1999, p. 6), "There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs." More recently, a study by Jan van Ours of Tilberg University in The Netherlands, which will be published by the Centre for Economic Policy Research in London, also concluded that cannabis is not a gateway drug (Sunday Times 2001). It is not the cannabis that is associated with progression to other illicit drugs, but rather its illegal status that makes it a gateway drug.

When compared to the legal and regulated drugs such as alcohol and tobacco, cannabis is much less harmful. I have worked as a registered nurse for more than 25 years in acute care facilities and during the past 10, I have served as the addictions consult nurse in a university hospital setting. During that time I have had the typical nursing experience of caring for persons who were hospitalized as a result of their drug use. Common reasons for admissions related to alcohol abuse include: traumatic injuries secondary to acute intoxication (motor vehicle accidents, falls, fights, etc.), overdose with alcohol alone or in combination with other drugs/medications, life-threatening alcohol withdrawal, pancreatitis, liver disease, gastro-intestinal bleeding, cardiomyopathy, cardiac arrhythmias secondary to acute intoxication, depression, suicide attempts, various cancers, and malnutrition. Common admissions related to tobacco dependence include: heart attacks, vascular diseases, pulmonary problems, and various cancers. Hospital admissions for cannabis related health problems are rare. Alcohol is responsible for more than 100,000 annual deaths, nicotine for more than 430,700 (Schneider In-

stitute for Health Policy, 2001), while use of cannabis has never killed anyone due to toxicity.

Driving under the influence of alcohol is the second leading cause for motor vehicle accidents after fatigue. While driving under the influence of any psychoactive drug is not recommended, several studies have shown that cannabis use does not seem to significantly impair driving performance and thus is not associated with an increase in accidents (National Commission on Marihuana and Drug Abuse 1972, Hunter et al. 1998, Bates and Blakely 1999, Frood 2002). It seems that drivers on cannabis tend to be aware of their intoxicated state and therefore drive more cautiously to compensate. The new study by the Transport Research laboratory in England did find that drivers under the influence of cannabis showed impairment in their tracking ability (being able to hold a constant speed while following the middle of the road), but those with a blood alcohol level of 50 mg/dl (0.05 g) showed even more impairment (Frood 2002).

In 1996, two leading experts in psychoactive drugs rated 6 commonly used drugs (Hilts 1994) (Table 1). Henningfield and Benowitz ranked nicotine, heroin, cocaine, alcohol, caffeine, and marijuana according to their potential risks for withdrawal symptoms, reinforcement, tolerance, addiction, and intoxication. They rated marijuana as the least serious risk, except for intoxication in which they both ranked it above caffeine and nicotine.

In recent years, treatment programs have had an increase in admissions for "marijuana dependence." The reason for this increase seems to be due to the fact that individuals charged with marijuana offenses (usually simple possession) are offered a choice of incarceration or treatment. Most choose to stay out of prison and enter treatment for "marijuana dependence." Just recently, the current director of the Office of National Drug Control Policy (ONDCP), John Walters, spoke to 4,500 teens and adults at the Pride World Drug Prevention Conference in Cincinnati. He told the audience that 65% of drug-dependent people have a primary or secondary dependence on marijuana and that (Kranz 2002), "Marijuana is two-thirds of the addiction problem in America today . . . We have too many people trapped in addiction to marijuana because they thought it couldn't happen, or they were told it couldn't happen." Where did these numbers originate? Drug experts Henningfield and Benowitz ranked marijuana as the least likely to lead to addiction or dependence. Inquiries made to the ONDCP asking for the source of these figures have remained unanswered. The IOM report (1999) concluded that marijuana is not highly addictive. Hopefully the American public will not accept these gross exaggerations.

One must ask the question that given the health and social risks related to alcohol and tobacco, which are regulated drugs for adult use, why isn't cannabis regulated for adults to use as well? Politicians, such as Representative Barr and Senator Feinstein, have justified the continued marijuana prohibition by rationalizing that we simply shouldn't add another *dangerous* drug for adults. From a

TABLE 1. Ranking of Risk of 6 Commonly Used Drugs

	Withdrawal		Reinforcement		Tolerance		Dependence		Intoxication	
	NIDA	UCSF	NIDA	UCSF	NIDA	UCSF	NIDA	UCSF	NIDA	UCSF
Nicotine	3	3	4	4	2	4	1	1	5	6
Heroin	2	2	2	2	1	2	2	2	2	2
Cocaine	4	3	1	1	4	1	3	3	3	3
Alcohol	1	1	3	3	3	4	4	4	1	1
Caffeine	5	4	6	5	5	3	5	5	6	5
Marijuana	6	5	5	6	6	5	6	6	4	4

Ranking scale: 1 = Most serious 6 = Least serious

Explanation of terms
Withdrawal–Presence and severity of characteristic withdrawal symptoms.
Reinforcement–Substance's ability, in human and animal tests, to get users to take it repeatedly, and instead of other substances.
Tolerance–Amount of substance needed to satisfy increasing cravings, and level of plateau that is eventually reached.
Dependence (Addiction)–Difficulty in ending use of substance, relapse rate, percentage of people who become addicted, addicts self-reporting of degree of need for substance, and continued use in face of evidence that it causes harm.
Intoxication–Level of intoxication associated with addiction, personal, and social damage that substance causes.

By Dr. Jack E. Henningfield of the National Institute of Drug Abuse (NIDA) and Dr. Neal L. Benowitz of the University of California at San Francisco (UCSF), data from an article in the *New York Times* (August 2, 1994, p. C3).

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harm reduction perspective one would have to ask, why wouldn't it make sense to allow adults to choose to use cannabis, a drug that is much less harmful (this is not to say it is *harmless*) to individuals and society?

CANNABIS PROHIBITION CAUSES MORE HARM THAN THE DRUG

Cannabis is the most commonly used illicit recreational/social drug in the US. Today, at least 76 million Americans have tried it (Substance Abuse and Mental Health Services Administration 2000, p. G-4). Many of those Americans who have risked "breaking the law" by using cannabis have suffered harsh consequences. In 2000, 46.5% (or 734,497) of the 1,579,566 total arrests for drug

abuse violations were for cannabis. Of those, 88% (or 646,042 people) were arrested for possession alone (Federal Bureau of Investigation 2001). With mandatory minimums for drug offenses, the prison sentences for cannabis convictions can be as long as several decades to life. Why are we willing to spend so much on prison terms for non-violent marijuana offenders? Are they truly such a danger to society that we are willing to take away their freedom and pay up to $40,000 per year per individual in prison costs? Would it not be wiser to allow them to continue to work and pay taxes? Couldn't this money be better spent by using it for drug addicts who are seeking treatment?

Children may be removed from their homes because a parent has been convicted of cannabis possession. Family members convicted of cannabis possession have been sent hundreds to thousands of miles away to serve time in overcrowded out-of-state prisons. These non-violent cannabis prisoners are often at the mercy of hardened criminals and suffer rapes, assaults and even death while in prison. Are they such a danger to society that we are willing to destroy the lives of these individuals and break up their families?

The Shafer Commission was very clear in their conclusions that such punishment was unwarranted (p. 78): "Neither the marihuana user nor the drug itself can be said to constitute a danger to public safety," and (p. 96), "Most users, young and old, demonstrate an average or above average degree of social functioning, academic achievement, and job performance." The Commission concluded (p. 41), "The most notable statement that can be made about the vast majority of marihuana users–experimenters and intermittent users–is that they are essentially indistinguishable from their non-marihuana using peers by any fundamental criterion other than their marihuana use." Yet hundreds of thousands of Americans remain behind bars separated from their families because of the marijuana prohibition. Readers may consult the web site of Families Against Mandatory Minimums (FAMM) for more information (www.famm.org).

Drug testing in the workplace remains a controversial issue. Most government organizations and private companies that perform drug testing conduct urine drug screens. To many this testing is an invasion of privacy, especially when done as a pre-employment requirement or random on-the-job testing. Urine testing is not a screen for drug abuse, it only tests for past drug use. There are numerous issues associated with drug testing, but cannabis poses a particular problem. The metabolites from THC are fat-soluble and can remain in the body for up to a month after the last use. Alcohol, in contrast, can be out of the system in a day (and is often not even included in the urine screen). Countless numbers of citizens have lost an opportunity for employment or been fired from their job based solely on a drug screen positive for cannabis.

There are waiting lists at many drug treatment facilities. Cannabis users who have been coerced into treatment by threat of incarceration or job loss are filling the openings that could and should be available for persons whose lives have

been destroyed by their drug addiction. This is not to say that no cannabis users may be in need of help, but rather there are alcoholics, IV drug addicts, crack cocaine addicts and others who have lost all control and are desperate for help that are turned away because there is no room for them.

The policy of prohibition interferes with the procedures necessary for quality control of this medication/drug necessary to prevent the risks of infection or other untoward reactions resulting from a contaminated product. Patients (especially AIDS patients) can suffer from a respiratory tract infection if the cannabis becomes moldy with the *Aspergillus* fungus (Krampf 1997, McPartland, Clarke and Watson 2000). Patients/users can also suffer toxic effects of other contaminants such as Paraquat, a highly toxic herbicide that was used by the federal government to destroy marijuana crops (McPartland, Clarke and Watson 2000).

The therapeutic use of cannabis could greatly reduce the financial costs to patients when they are able to eliminate other medications. The cost of therapeutic cannabis should be minimal in a regulated environment. However, prohibition has inflated the price of cannabis to that of gold. More important than the financial costs, patients who could benefit from the therapeutic use of cannabis are denied this medicine that may help them when all other medications have failed. There is no excuse for denying them the option of trying this medicine.

Denying patients access to therapeutic cannabis does nothing to prevent substance use/abuse among adolescents. The government claims they are concerned about drug abuse among our children and that by acknowledging the therapeutic potential of cannabis they would be sending the wrong message to our youth. Rather, the continued prohibition sends other more chilling messages to our youth: Their government is willing to put patients in prison simply for taking a medicine to ease their suffering. Their government will ignore, try to cover up, or lie about scientific studies that do not support its unjust policies/laws. If their government is lying about cannabis, what else is it lying about?

Finally, cannabis prohibition interferes with open communication between patients and their healthcare providers (Mathre 1985). Patients fear talking to their primary care provider because of possible negative reactions. Patients don't want their use noted in their health record because they fear there may be legal consequences. This fear of admitting to cannabis use to their healthcare provider interferes with the development of a trusting relationship. Healthcare professionals cannot adequately monitor the effects of cannabis if they aren't aware of its use. Health care professionals cannot educate the cannabis user about the potential risks of cannabis if they are unaware of its use.

CONCLUSIONS

The possibility of a "drug free" society is unrealistic. People seek and use drugs to feel better. Medications/drugs are not risk free, but the risks can be mini-

mized only with accurate and readily available information on the harmful effects prior to their use. Compared to most medications available today, cannabis is remarkably safe and effective and therefore should be available as an initial option to patients. As a social/recreational drug, the effects of cannabis are pleasant for many with little personal or societal risks and therefore may be the safer choice compared to other social/recreational drugs used by adults. While concern is justified about the dangers related to children and teenagers using drugs, the lies and cruelty of the marijuana prohibition are confusing to young people who learn not to trust their government. The harm resulting from the prohibition of cannabis costs individuals and our society as a whole much more than the drug itself.

When viewed from a nursing perspective, cannabis can be a useful therapeutic agent if it were legally available. Cannabis could be a useful harm reduction agent for substance abuse if it were regulated. The greatest harm from cannabis is the threat of legal consequences related to its illegal status. Nurses and other health care providers can play a vital role in reducing the harmful effects from medication/drug use. Health care professionals can teach patients and the public how to minimize the potentially harmful effects of cannabis when it is used as a medicine or social/recreational drug, but as long as cannabis remains in Schedule I, health care providers will be reluctant to talk with their patients about this drug. The role of the health care provider is severely compromised by cannabis prohibition and society suffers from this unjust, cruel, and costly policy.

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Crack Heads and Roots Daughters: The Therapeutic Use of Cannabis in Jamaica

Melanie Dreher

SUMMARY. An ethnographic study of women and drug use in inner city neighborhoods in Kingston, Jamaica, revealed that cannabis is commonly used in conjunction with crack cocaine to minimize the undesirable effects of crack pipe smoking, specifically paranoia and weight loss. According to 33 current or former crack using women, who were followed for a period of nine months, cannabis cigarettes ("spliffs") constitute the cheapest, most effective and readily available therapy for discontinuing crack consumption. The findings of this research suggest the need to reframe "multiple drug use" within the cultural meanings that attend cannabis in Jamaica as a medicine and a sacrament. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www. HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Cannabis, ganja, culture, crack, cocaine, Jamaica, women, self-treatment, Rastafarians, multiple drug use

There are only two illicit substances that are widely used in Jamaica, marijuana (or "ganja," as it is called locally) and crack cocaine. This paper describes the use of cannabis as a cheap, available therapy for the treatment of cocaine ad-

Melanie Dreher, PhD, FAAN, is Dean and Professor, University of Iowa College of Nursing, 101D Nursing Building, 50 Newton Road, Iowa City, IA 52242-1121 (E-mail: melanie-dreher@uiowa.edu).

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diction by working class women in Kingston, Jamaica. The findings reported here are derived from an ethnographic study of crack-using women in Kingston (Dreher and Hudgins 1992). The purposes of this study were to identify the social and economic conditions that promote and reinforce cocaine use and generate implications for treatment and prevention. Complementing the earlier large-scale opinion survey that had influenced drug policy in Jamaica (Stone 1990), the ethnographic design was deployed to: (1) observe the actual drug-linked behavior of crack using women in the natural settings of home and community, (2) permit a longitudinal examination of the processes embedded in drug careers over several months, and (3) overcome the potential mistrust of investigators that often accompanies research on illegal and socially sensitive activities.

Participant observation in inner city Kingston provided opportunities to witness, first hand, the social interactions and behavior associated with crack consumption and procurement, the daily routine of crack users, the techniques of crack cocaine ingestion, and the role and status of crack users in their communities. In addition to the general observations in the homes, yards, and community establishments of a Kingston neighborhood, 33 women who had ever used cocaine and its derivatives were followed for a period of nine months, in which their drug use and life events were monitored and recorded. An unstructured interview schedule served as a guide for the investigators, ensuring the comparability of the data while not constraining the responses of informants. As their histories unfolded, probes by the investigator generated new factors that were added to the interview schedule and explored in repeat visits to all participants.

The data derived from both interviews and observations included: (1) socio-demographic characteristics such as age, place of birth, residence, transience, religion, education, employment, marital status, health status and ethnicity; (2) past and present social relationships including family of origin, conjugal unions, children, household composition, friends, and recreational activities; (3) major life events; and (4) drug use careers including the circumstances surrounding initiation to crack, current use patterns, perceived short-term and long-term effects of crack use and their opinions of crack as both a personal and social phenomenon. Their wealth of experience and their willingness to share it provided us with a window into the drug related behavior of women in Jamaica.

GANJA

Although the use and distribution of ganja (cannabis) are illegal in Jamaica, the substance has been part of Jamaican working class culture for over a century (Rubin and Comitas 1975; Dreher 1982). There is a strong cultural tolerance for ganja and for most of the working class, it simply is not regarded as a "drug" (Dreher and Shapiro 1994). The Rastafarian community has adopted ganja as its

sacrament–substance "from the earth," in harmony with the environment, natural (or "ital") and indigenous. Even heavy cannabis users, such as Rastafarians, are accepted because they do not threaten the social fabric of the community.

The use of cannabis for therapeutic purposes is not new in Jamaica. For over a century, the health-rendering properties of cannabis have enjoyed widespread endorsement (Rubin and Comitas 1975; Dreher 1997). Ganja tonics, teas and other infusions are household medicines used both curatively and prophylactically by Jamaicans of all ages, both sexes and a wide range of socioeconomic levels. Believed to improve health, stimulate the appetite, enhance work, promote a calm, meditative approach to life, reduce violence and augment sexual performance, ganja is a substance that symbolizes and promotes enduring values about health and behavior in Jamaica. Over the years, socially generated rules have evolved regarding who can use ganja, when, where, in what form and how much, creating a "complex" of social institutions that have served to guide the use of ganja and inhibit its abuse.

For example, since its introduction to Jamaica in the mid-nineteenth century by indentured laborers from India, ganja smoking, either in a "spliff" (ganja cigarette that is sometimes mixed with tobacco) or a pipe (also called a "chillum" or "chalice"), has been almost universally a male-dominated activity. Indeed, the early anthropological studies of cannabis use in Jamaica, conducted in the late sixties and early seventies, focused on ganja smoking as a working class, male social activity (Dreher 1976, 1982; Rubin and Comitas 1975). The female ganja smoker was rare, except in a pre-sexual context with their mates, and the few women that did smoke ganja outside of socially prescribed contexts were regarded as disreputable and often held in contempt by both men and women in their communities (Dreher 1984).

The organization of consumption based on sex was validated by the ethno-physiological explanation that ganja, when smoked, goes "directly to the brain," producing psychoactive effects that include the power to "reason" or engage in intellectual and philosophical discourse. In contrast, when drunk as teas or tonic, goes "directly to the blood," where it promotes health, prevents disease, and makes the body strong and ready to work. According to the men who smoked ganja, women "do not have the brains" for smoking and were excluded from the adult recreational and work groups in which ganja was used and exchanged socially. At the same time, however, it was usual and acceptable for women to cultivate and sell ganja, and even more common for women to prepare and administer ganja in the form of medicinal teas and tonics to their families and household members (Dreher 1984).

The institutionalized social rules that comprise the ganja "complex," including the widespread sanctions against female smoking, have continued to limit use among women. Within the past twenty years, however, increasing numbers of women have begun to smoke ganja routinely, in a manner not unlike their male

counterparts. Partly due to the increase in Rastafarianism, not only are such women tolerated, but many have been given the commendatory title of "roots daughter" (Dreher 1987). The term "roots" has become part of the Rastafarian and youth vernacular in Jamaica to signify that which is real, natural, original, perhaps African, or at least, non-Western. The appellation "roots daughter" is used to identify women who come from a fine, if humble, tradition, who have "good brains," who can "smoke hard as a man" and with whom men can "reason" (discuss and debate) as they would with other men.

The roots daughter is not simply a ganja smoker but also a clear thinker and a woman of dignity. She "must keep a standard" and "go about properly." If she is involved in a stable union, her partner can expect her to be helpful and sexually faithful. As one informant explained, "if your woman is roots and you see her talking to another man, there is no reason to be jealous." Roots daughters are dignified, conservative, independent, non-promiscuous, hardworking and spiritual. They often are contemptuous of jewelry and make-up and may be recognizable by their hair, which frequently is styled in dread locks and covered. Finally, a roots daughter is a responsible, strict but nurturing mother who values education (both intellectual and moral) and who will forego her own ganja smoking to prepare ganja teas and tonics for her children to "make them smarter and stronger." Nevertheless, roots daughters are not the norm and the restrictions on female ganja use in the general population remain intact.

COCAINE

The presence of cocaine, especially in the form of crack, is relatively recent in Jamaica. Unlike the "ganja complex," with its institutionalized social rules that guide use, there is no "culture" for crack cocaine. Explosive rates of addiction have resulted in widespread social and economic dysfunction (Dreher and Hudgins 1992, Dreher 1995). Cocaine is chemically prepared, synthetic and not indigenous to Jamaica. Crack users, in general, are considered inherently "repulsive," straying from what is considered "normal" human behavior. For most Jamaicans, the use of crack cocaine is not only a violation of the law, but indicative of an undisciplined, lazy and even unhygienic person. In a society that values "clear" skin, fleshiness, sexual vigor, self-control and family loyalty, the "mawga" (skinny), debauched, impotent crack user is seen as fundamentally "bad," violent, self-serving, and the antithesis of everything that is good and important in Jamaica.

In Jamaica, crack is consumed in two ways: either directly in a pipe, or ground and sprinkled on a ganja cigarette, called a "seasoned" or a "dust up" spliff. In a seasoned spliff, the rock (crack) is mashed and spread over the mixture of ganja and tobacco, which is then rolled and smoked. Some users sprinkle the ashes

from the pipe on the seasoned spliff so as not to waste any part of the crack. The seasoned spliff is of particular interest because it is the form of drug consumption in which two opposing Jamaican metaphors intersect: ganja (the wholesome multi-purpose herb) and crack (the noxious drug).

Opinions regarding the "seasoned spliff" are mixed and reflect the beliefs and behavior of the users. Rastafarians, with their ideological commitment to ganja as a sacrament, disdain the idea of mixing crack cocaine (a white man's poison, an unnatural substance) with a natural substance that is associated with physical and mental health and is considered indigenous to Jamaica. Almost universally, they regard the seasoned spliff as "defiled herb," alleging that it is the signature of "commercial Rastas" or "Rasta-tutes," who earned their livelihood by being the sexual partners of American and European female tourists.

Ironically, many crack pipe users were equally derisive of the seasoned spliff, claiming that herb (ganja) weakens the effects of the crack: "Real crack users aren't interested in the seasoned spliff." "Real crack addicts are not interested in ganja at all." "Wi' de pipe, you feel de effects instantly." "Me prefer de blow." According to one self-identified coke addict, she didn't like the seasoned spliff because when she smoked it, it made her feel like her "mind is beatin' (racing), but when you smoke it in a pipe it makes you feel numb."

Based on the results of his national survey, Stone (1990) attributed the increase in crack cocaine use to the seasoned spliff, asserting that ganja is the "gateway" to cocaine use. In the sense that ganja established inhalation as the primary mechanism by which to achieve a psychoactive experience (intravenous drug use is rarely, if ever, practiced in Jamaica), crack smoking clearly fit well into the existing Jamaican drug paradigm. The gateway explanation is further reinforced by reports of vendors "seasoning" ganja to create a more potent product and thus a market for cocaine. On the other hand, the almost universal presence of ganja smoking and the comparatively small percentage of crack cocaine users suggest that there is no direct or necessary relationship between ganja and crack and, at the very least, call for further analysis.

WOMEN AND CRACK

Unlike ganja, crack routinely is consumed with members of the opposite sex, and thus the most likely explanation for the higher proportion of women among crack smokers than that among ganja smokers. In some Jamaican communities women are reported to make up 25% of the crack users (Dreher and Shapiro 1994). Several women reported that they first were exposed to cocaine by "big men," such as entertainers, who allegedly are responsible for introducing literally hundreds of young women to cocaine. Women who are directly or indirectly associated with the tourist industry are most at risk (Broad and Feinberg 1995). As

one study participant stated simply, "tourists like to try different drugs when they are on vacation." Thus, women who are hotel workers or waitresses, as well as exotic dancers and prostitutes, are recruited to procure crack for tourists and are likely to be invited to join them in smoking it. Women who are associated with men who work in tourism and the entertainment industry also are at risk. Taxi drivers, for example, often are asked to obtain crack/cocaine and then are invited to partake with their female tourist customers. They, in turn, may take some home for their girlfriends to try and even turn to selling crack/cocaine themselves.

In contrast to roots daughters, women who smoke crack are considered drug addicts and held in the very lowest esteem. To support their dependency, the vast majority of crack addicts become street prostitutes and engage in sexual practices that are outside normative behavior for Jamaicans, including oral sex, anal sex, and performance sex with other women. Female crack users in Jamaica suffer a life of peril and degradation. Prostitutes reported being beaten, stabbed, and robbed by their clients. In addition they are exposed to HIV infection and other sexually transmitted diseases. Moreover, their exposure to danger is increased at the very time that their ability to avoid or manage high-risk situations is most impaired.

Of the 33 women who were followed in the study (Table 1), 17 were using crack in some form at the time of the study while 14 were former users. Of the 17 current users, five were exclusively pipe smokers, 11 smoked both the pipe and seasoned spliff and only one smoked seasoned spliffs exclusively. Of the 14 former users, only one had used the pipe exclusively, 7 were exclusively seasoned spliff users and 5 used both pipe and seasoned spliff. The remaining former user was the only woman in the study who "snorted" cocaine powder while she lived abroad but had not used cocaine since she had returned to Jamaica and became a Rastafarian. The eight women who used the seasoned spliff exclusively, typically defined themselves not as crack *addicts* but rather as crack *users*, for whom the seasoned spliff was enhanced herb, with an extra "kick" or "boost." In contrast, all the pipe smokers, whether they used it exclusively or in addition to a seasoned spliff, identified themselves as addicts.

All the women in the study agreed that the two modes of ingestion produced very different effects. As one woman stated, "the pipe makes you more high than dust spliff." She recounted how she likes to smoke a seasoned spliff and that her capacity to "reason" was facilitated by the mixing of crack with ganja. Another woman stated that the pipe made her feel "more drunk," "like a monster." She also said that it will make you "grow fine like a thread" (thin), if you continue to use it alone. The youngest user in the study, who smoked only seasoned spliffs, commented that the "pipe do you bad–mek you want it more often." Both kinds of crack users believed the pipe is more addicting than a seasoned spliff or even "snorting." Many of the women who had smoked crack in a seasoned spliff for several months or even years, reported that when they were exposed to the pipe, it

TABLE 1. Crack/Cocaine Using Women in Kingston, Jamaica According to Type of Use

	Current Users	Former Users	Total
Pipe	5	1	6
Seasoned Spliff	1	7	8
Combined	11	5	16
Intranasal	0	1	1

quickly became their predominant and preferred mode of use. One woman described how cocaine was pushed on her by a "guy who dust up a cigarette" and gave it to her. She said she refused it several times but he was persistent and finally she tried it. Because she had experienced little danger in the seasoned spliff, she started smoking the pipe, which she now uses exclusively. Thus while crack and ganja commonly are thought of as linked in both consumption and distribution, participants in this study saw them as quite distinct. "The difference between ganja and coke is that with the ganja you can still work, cook and clean up . . . When you're high on ganja you want to eat but when you are high on coke you don't want to do anything. You are just afraid and want to hide."

The devastating impact of crack on their health and physical appearance, typical of crack users cross-culturally (Ratner 1993; Inciardi 1993), was a consistent complaint of participating women. Not only does crack "rob" them of their strength and ability to work, it impairs their appearance with dry hair, dark blotches and sores on their skin, burned and stained fingers, and, perhaps most important for this Jamaican population, severe weight loss. In addition to the physical effects of crack, the women reported a disregard for personal hygiene and grooming, including hair, skin and clothing. Regardless of their family history or social status, they reported stealing from and lying to their friends and relatives and being referred to as "coke heads" or "crack heads," universally despised and disrespected. Many of the women in the study were banished from their home communities and one woman reported that her mother threw a pail of boiling water at her as she approached her family home, where her children were living with their grandmother. As prostitutes, they engaged in sexual practices that others found repulsive and it was not unusual for young boys to call them names, e.g., "suck hood," or "lick 'im batty" (referring to fellatio and oral-anal sex), or even to stone them. The combination of community distrust and repulsion reinforced their social isolation and self-loathing.

Both current and former crack using women lamented their waste of money. Although they had the potential to generate comparatively large sums of money

in a very short period of time through prostitution, they reaped no permanent benefits. They stated repeatedly that their need for crack supersedes all other needs, including food, clothing, housing and child support. Indeed, it is the impact on their children that was the most compelling source of guilt and remorse. Children had to be placed with other family members, friends or even neighbors because of the mother's inability to care for them. Women poignantly described having their children removed by police, subjected to ridicule by community members, neglected and abused both physically and sexually, often by their prostitution clients.

Consistent with the literature on women cocaine users in general (Pottieger and Tressell 2000), children were a primary motivation for these Jamaican women to discontinue cocaine use. One former crack user, for example, discontinued her habit one month before her first grandson was born because she did not want her grandchild to "come and find his granny a prostitute and a drug addict." During the interview, one of her children brought her grandchild in to her. As he sat on her lap during the interview, she caressed his head and smiled, "he's my drugs, I know I am not going back, I have control and I love my grandson and my kids." A few women reported that they had stopped smoking during their pregnancies because they heard that their addiction might kill the baby.

Also consistent with reports from other cultures (Labigalini et al. 1999), the drug histories of these women did not fall into a uniform trajectory, moving singly and consistently from non-use to addiction and then, if they recovered, back to non-use. It was not unusual, for example, to refrain from smoking for a few days, or even weeks, while they visited their families or when they felt that they were getting too thin. Many used a trip to their family home, usually outside of Kingston, as an opportunity to "stay clean" and "fatten up." Some women, who had been ostracized by their families, and thus could not go home, reported actually trying to get arrested so that they would be incarcerated and could sleep and get three meals a day. A short jail sentence was a welcome relief from sex work and provided an opportunity to gain weight.

While their children, family members, and communities were powerful motivators for these women to discontinue crack cocaine, they also reported that such motivators were insufficient to maintain abstinence for long periods of time. In most cases, the return to crack use generally was triggered by a personal problem or simply because they were depressed and wanted to feel better. One participant, for example, reported that her boyfriend got her pregnant to get her off coke and she was clean for one year and three months but she started using it again when he returned to Jamaica with his wife. Another woman, working as a prostitute, said that she had stopped for four months and then started back when a client paid her with crack.

With the exception of the youngest participant in the study, who used only the seasoned spliff, all current users longed to discontinue smoking crack permanently

and get their lives in order. Most were uninformed of any treatment facilities available to them. Four had tried to enroll in the University of West Indies Hospital drug intervention program but had been put on waiting lists of several months. In fact, treatment and counseling programs in which these women could avail themselves of professional assistance were almost non-existent.

Given the unavailability of formal detoxification and recovery programs in Jamaica, the experience of the 14 former users is both important and cogent. Of the fourteen, one was an intranasal cocaine user while living abroad who became a Rastafarian on her return to Jamaica, gave up cocaine and now partakes of ganja as a religious sacrament. One was a woman who had never used ganja and was the only participant who had received professional assistance. Of the remaining 12, seven had been exclusively seasoned spliff users and five were pipe users who also smoked seasoned spliffs. Of these last five, three started using ganja for the express purpose of reducing the cravings, the paranoia and the loss of appetite associated with crack use.

Labigalini et al. (1990), reporting a similar folk therapy in Brazil, described the experience of several male patients in a treatment program who had used cannabis to reduce their craving for crack, thus helping them to overcome their addiction. According to these authors, the control of impulsive behavior and stabilization of the hunger mechanism is likely explained by the capacity of cannabis to increase the cerebral availability of serotonin that has been compromised by crack cocaine. Indeed, there were numerous reports from both ganja and crack users that ganja slows down the immediate effects of crack, and makes the overall high less intense but last longer and trail off more gradually. This avoids both the plummeting euphoria and subsequent paranoia that precipitate the need to smoke again. According to one woman:

> It makes me charged but not as strong as the pipe. It stays longer than the pipe–about 20 minutes to half an hour, while the pipe stays in your system for only ten minutes. The pipe is a killer . . . I was always wanting the next pipe. The seasoned spliff is much better to me than the pipe. You can eat and drink at the same time because the herb opens the appetite. When it wears off, I feel like I want a fresh (bath) and sleep. When you smoke season spliffs, you don't feel "paro." It is a different meditation. Crack and coke are like demons and devils, they are not good and to how dem see de pipe mash up people, dem a turn to season spliff and some a dem nah touch de pipe.

The opinion of some of the users was that ganja simply reduces the volume of crack needed for a high while others claim it has a psychological role in counteracting the triggers in the environment that stimulate the need for crack cocaine.

> It mek you meditate an' have an interest away from crack.
>
> . . . when you want crack you should smoke a spliff instead.
>
> . . . nuff time me would use crack but (ganja) mek me t'ink twice.
>
> . . . herb helps me not want to smoke.
>
> If you're trying to stop and you smoke weed, you nah wan de rock.
>
> With two spliff, I can resist crack.

The use of ganja as a vehicle for getting through the stress and urgency associated with the need for a "lick" of cocaine was reported by almost all of the women who were followed in this study.

Among the current users, the women who combined ganja consumption with their crack consumption were much more "successful" users in terms of physical health and lifestyle. In addition to reducing the need to smoke large quantities of crack, and thus engage in extensive and depleting prostitution, the role of ganja as an appetite stimulant was mentioned by several women. Even committed pipe smokers smoked ganja to compensate for the weight loss that accompanies cocaine use. Among the eight users (current and former) who smoked crack only in a seasoned spliff and did not consider themselves to be true addicts, all claimed that they were able to discontinue crack consumption easily and that they smoked a seasoned spliff because they enjoyed it, not because they needed it.

While the intriguing, preliminary evidence supports the physiological capacity of ganja to promote cocaine abstinence, its *cultural role* as a health rendering substance that induces thoughtfulness, meditation and communion with "Jah" (God) also warrants mention. Roots women, especially those with definitive Rastafarian affiliations, rejected a lifestyle requiring prostitution and culturally deviant sexual practices. Although there is no explicit injunction against crack in Rastafarian doctrine, the "roots" concept provides a comprehensive plan for living that includes responsibility, dignity and a family orientation. As the one Rasta woman in the study stated:

> Me nah trouble dat ting . . . me a roots. Now I am proud and happy to state that I am completely cured from that sin, and indeed, I am ever so thankful to Jah. Surely, God is good . . . A very common saying is that cocaine addiction is uncurable. I have proved that saying to be completely wrong. My advice to all who want to quit using that garbage is to sincerely ask Jah for his help.

Being a roots daughter provides the motivation not only to discontinue the use of crack cocaine, but to reduce exposure to the drug in the first place. As such, Rastafarianism, with the ganja sacrament, has ideological value for prevention as well as treatment. The only roots daughter among the 33 women in the study was the one informant who had used cocaine intra-nasally when she lived abroad some years earlier. Since she became a Rastafarian, using ganja sacramentally, she speaks in great opposition to crack cocaine. The effectiveness of religious involvement in the treatment of alcohol and drug addiction has been long acknowledged (Buxton et al 1987), and the notion that one substance can be used as a deterrent to, or replacement for, others is not new. Historical evidence suggests that peyotism, for example, provided an alternative substance as well as an alternative lifestyle, thus serving as a deterrent to alcoholism among Native American populations (Hill 1990). Even Sefanek and Kaplan (1995) reevaluated their "stepping stone" theory in the light of Dutch heroin users who succeeded in controlling the damaging effects by smoking cannabis.

CONCLUSIONS

Although the evidence is preliminary, the reported success rate of self-cure, using the cheapest and most available psychoactive substance, is persuasive. It lends credence to the reports of male crack users in Brazil and heroin users in the Netherlands and, at the very least, deserves further investigation. The data certainly suggest that ganja is neither a precondition nor a gateway to crack use. In fact, nine of the 33 women had never used ganja at all and reported hating "even the smell of it." Although the majority of the participants in the study had smoked ganja prior to using crack cocaine, the number of years elapsing between initiating crack use ranged from one to thirteen, suggesting no automatic or direct linkage either physiologically or socially between ganja and crack. The youngest woman in the study (16 years old), said that she *started* using a seasoned spliff because her boyfriend wanted her to try it but spoke adamantly against pipe use. Moreover, for the women who were ganja users prior to becoming crack users, the number of years elapsing between initiating crack use ranged from one to thirteen, suggesting, again, no automatic or direct linkage.

Indeed, these findings indicate that rather than serving as a gateway to crack, cannabis may be instrumental in both the prevention and treatment of crack addiction. Of the 14 women who succeeded in discontinuing crack use, 13 attribute their success to the use of ganja, either because of its capacity to control the damage of crack cocaine use physiologically or, in one case, because of its religious value. Moreover, it is clear that the women who combined ganja and crack were at least able to maintain their weight and care for their children. At the very least, these findings beg the need to revisit the notion of multiple drug use in a more

culture-specific context. Far from being the hedonistic multi-drug users that present so many challenges to prevention and treatment programs, the women in this study were actually self-medicating, either to modify the effects of pipe smoking or to relinquish the habit all together.

IMPLICATIONS

Crack is a highly addictive form of cocaine, with serious social consequences. The exponential increase in crack use worldwide has generated an urgent demand for treatment and prevention programs and international development agencies in the United States have invested considerable monetary and technical support to develop such programs in Jamaica as well as other countries. It is common knowledge, however, that health and social service programs are not automatically transferable from one society to another. Effectiveness requires that such programs be designed according to what is meaningful and important in the culture where it is to be applied. Thus the commitment to demand reduction and treatment programs by both the Jamaican and United States governments has created a need for continued monitoring of the knowledge, attitudes and practices surrounding substance consumption and distribution. Not only is ganja typically not thought of as a drug in Jamaica, it has assumed a positive value for limiting the ravages of cocaine as an appetite stimulant that counteracts the anorexia of cocaine addiction, and as an assistive substance in relinquishing cocaine addiction. Yet the tendency to include ganja, often as a starting point, for drug prevention and intervention in Jamaica continues to exist. Whether or not the use of ganja is a remedy for crack addition in the biological, psychological or sociological sense, programs that fail to acknowledge the different cultural meanings and experiences attached to these two illicit substances ultimately will lose credibility with the very population they need to serve. The experience of women who have managed to relinquish their cocaine habit without expensive professional intervention would appear to be highly consequential for the design of effective, low cost, culture-specific treatment programs both in the United States and internationally.

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One Woman's Work in the Use of Hashish in a Medical Context

Mila Jansen
Robbie Terris

SUMMARY. This article provides a brief introduction to the process of producing hashish with the Pollinator® and Ice-O-Lator® devices. Both are systems designed to separate the most active parts of the cannabis plant, the glandular trichomes, or "resin glands," from the plant material. The highly concentrated product of these systems has great value to medical users of cannabis, as they only need to employ a fraction of the amount of material otherwise necessary. The systems can also be used to pre-process cannabis or hemp for laboratory work that requires solely the active substances. The article also gives a brief introduction to Mila Jansen, the inventor of the Pollinator and the Ice-O-Lator. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www. HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Hashish, Pollinator, Ice-O-Lator, cannabis genetics, medical marijuana

There are several definite benefits to employing hashish as opposed to herbal cannabis, especially in a medical context. If one examines a female cannabis

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Mila Jansen and Robbie Terris are affiliated with the Pollinator Company, Nieuwe Herengract 25, 1011 RL Amsterdam, Holland (E-mail: info@pollinator.nl) (Web: www.pollinator.nl).

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flower under a microscope (20X), the bulk is the plant material with several thin pedestals on the surface called glandular trichomes. Atop of each stalk is a tiny clear resin gland, or head, that is the component of the flower that contains approximately 90% of the active cannabinoid ingredients: tetrahydrocannabinol (THC), cannabidiol (CBD), other cannabinoids and essential oils with a variety of therapeutic terpenoid components (Clarke 1998). The concentration of these tiny resin glands into what is traditionally called hashish is a logical step when seeking a medical application of cannabis. The chemical potency will be enhanced, and levels of active ingredients will be consistent throughout all of the collected material, therefore making it easier to administer accurately in precise dosages. Extraneous fiber components unnecessary to therapeutic effects are also eliminated.

Hashish was traditionally made in many eastern countries. The primary author was lucky enough to be in Morocco in 1965 and in Turkey, Afghanistan, Northern Pakistan, India and Nepal in 1968-69. The techniques for making hashish were distinct in each of these areas. We learned to make our own, either sifting or hand rubbing the flower buds. There were government hashish shops and temples in Nepal where patrons smoked the *goolies* (balls) of hand rubbed hashish with the *babas* and *saddhus* (holy men, wandering ascetics on life long pilgrimages, smoking hashish, devoting their lives to Shiva, the Hindu God of destruction of ignorance). There, hashish is a holy sacrament. There are rituals, mantras, *mudras*, meditations and visualizations connected with the smoking of a chillum (straight clay pipe). Hashish is an age-old medicine that is also used by many cultures as a means of social and spiritual development.

Eventually, I settled in Northern India with my four children for a number of years. After coming to live in Amsterdam in 1988, I found that most cannabis users smoked marijuana and there was very little good hashish available, so we set about trying to make some of our own. We would store all the dried leaf material until the coldest nights in winter, the extreme cold being ideal for extracting the resin glands, making them easier to isolate. The leaf material would then be gently tossed over a silk screen to knock off the resin glands for collection on a smooth surface beneath. This process, taken from the ancient method employed in Afghanistan for thousands of years, was time consuming and laborious. We continued the technique until 1993, when inspired by my clothes drier, I invented the Pollinator® machine.

The Pollinator machine is a dry method of resin gland separation, which contains a removable drum that is opened for the insertion of leaf material (Figure 1). Inside the rim of the drum are several horizontal rods which further aid the tumbling of the leaf material. The drum is closed and placed back inside the Pollinator where it is turned by an electric motor. Low temperature and low humidity are crucial when using the Pollinator machine, as both these factors greatly increase the yield and the quality of the collected product. Quality of any

FIGURE 1. Mila Jansen with Pollinator® drums.

hashish or other cannabis based product is primarily genetically determined. The chemical make up, yield and other such traits are all genetically influenced. The main concern is how to extract the resin glands from the plants as cleanly and efficiently as possible. By placing the leaf material in an airtight container, which is then placed in a freezer for two hours, one may approximate the low temperature

necessary but the humidity will not be sufficiently low. We discovered that when the outside temperature was −10°C the Pollinator produced the best quality product in the shortest time period. Extreme low humidity combined with literal freezing of the resin glands produces a very clean removal of the glandular trichome heads from their brittle stalks. In an environment with a warmer working temperature, there will be a significant decrease in the quality of hashish collected as a result of a greater proportion of stalks and other small pieces of plant material being present in the subsequent collection.

The resin glands from the cannabis leaves fall through the precise fine screen around the drum onto the bottom of the Pollinator container for later collection. The size of screen employed for the Pollinator is 147 μ, so as to allow the largest resin glands to fall through freely. The quality of the hashish is dependent on the length of time the drum is allowed to turn. A session of three to five minutes produces top quality hashish (containing only glandular trichomes without plant material, dirt or other impurities); longer turning results in a lower quality as the plant material is broken down and falls through the screen, mixing with the separated resin glands. The five minute turning of the Pollinator produced hashish that would have taken hours of labor-intensive work by traditional methods. This allowed Dutch growers of cannabis to make a small amount of excellent hashish easily from plant material previously considered waste.

The Pollinator was the first modern machine to be designed for the production of hashish. The industry was previously unchanged for thousands of years due to the fact that silk screens used for sieving had not been improved until the creation of modern technology. The first Pollinator machines were sold from home, but after a couple of years, I opened a shop as there was a clear demand by many cannabis growers who had marvelled at the first public demonstration of the Pollinator machine by Robert C. Clarke at C.I.A. Amsterdam, during the 1994 High Times Cannabis Cup event. This gave us more time and space to work on the development of methods to improve the technique of pure hashish production, as previously all the testing was done at the kitchen table. It was in this shop where I made my second breakthrough, the creation of the "Ice-O-Lator®," a water and ice method of making hashish.

In 1997, we practiced at home with jugs of water, but had no satisfactory results. The big revelation did not come until we saw the Extractor®. Designed in the USA, and manufactured in Yugoslavia, this system tended to break down within 8 months, and was very heavy and expensive. All over the world, people could buy buckets and mixing machines. In the summer of 1998, I sewed my first Ice-O-Lator bags.

This method of extracting the resin glands from the leaf material involved the use of water and ice (Figure 2). Leaf material is placed in cold water (4°C), where it is agitated causing the glandular trichomes to separate from the plant material. Temperature is again of great importance. As the herbal material is agitated in the

cold water, hardened resin glands are dislodged more cleanly. Gravity then plays its part as the trichomes sink, and the plant material is left floating on the surface. With the aid of two precise screens (one for the leaf material and the other for the resin) the desirable mature glands and leaf material are separated. One factor that influences the resin glands are ideal growing conditions. Resin glands from plants grown indoors are slightly larger than those grown outdoors, as the plants have more light, nutrients and water. For outdoor growers of cannabis (or older plants where the resin glands have shrivelled with drying), I prefer a 187 µ screen on top. This will allow the resin glands to pass through while containing the rest of plant material. A pore sized screen of 62 µ as a lower screen will trap the extracted glandular heads. For growers of indoor plants with larger sized glands, I recommend a top screen of 210 µ and a 77 µ screen for the lower bag.

The Ice-O-Lator process is very simple, quick and efficient. The process begins by hanging both Ice-O-Lator bags (making sure the bag with the larger pore sized screen is on the top of the fine screened bag) in a bucket and then adding the plant material, ice blocks and enough cold water to 3/4 fill the bucket. A temperature of between 2-4°C is set before starting to agitate the plant material and ice.

FIGURE 2. Washing machine Ice-O-Lator® with open drum, ice and cannabis in filter bag.

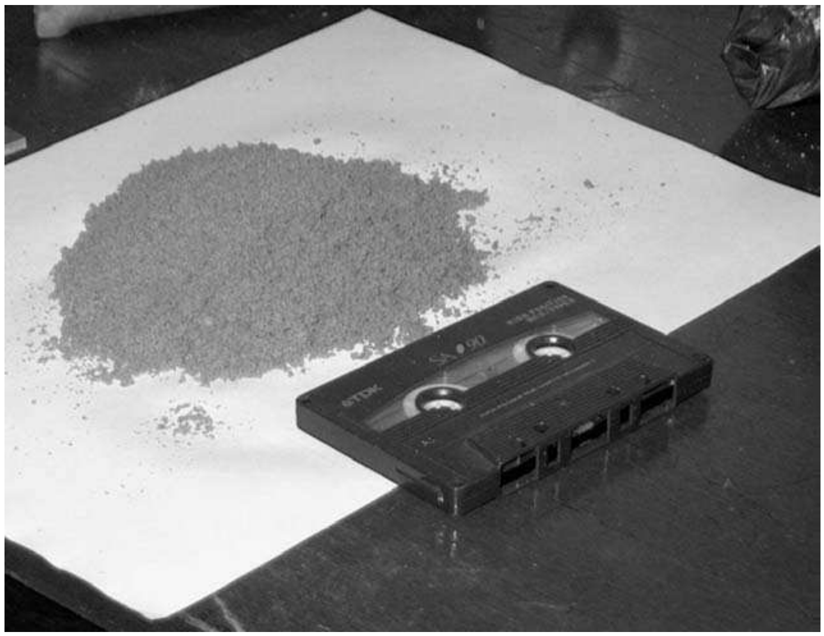
After twenty minutes of agitation, the water is left to settle for twenty minutes. In this period, the resin glands sink and any plant material rises to the surface. The top bag may then be gently raised out of the bucket, allowing the water and resin glands to drain. Lifting the lower bag out of the bucket reveals the collected trichomes once the water has drained. The inside of the bag is then rinsed with water to collect all the resin glands from the top of the screen. The outside of the bag is the wrapped in kitchen paper and pressed to remove the water. The resin glands are then sufficiently dry enough to remove from the Ice-O-Lator bag.

The collected resin glands are then placed into a metal kitchen sieve and filtered onto paper below. The resin glands are then ready for complete drying, as moisture may quickly lead to a deterioration of quality due to fungal growth. Once the resin glands are fully dried, they can be stored by pressing, or left in granular form (Figure 3). The Ice-O-Lator has proved to be the most efficient method of separation when taking into consideration factors such as time, purity and quantity. In the "coffee shops" of Amsterdam, the hashish made by this process is highly sought, as its potency and purity have become legendary. Ice-O-Lator bags have been sold throughout the world.

The Dutch Government awarded a research subsidy to the Pollinator Company in 2001 for the sole purpose of investigating resin separation methods for use in medical marijuana. As a medical commodity, cannabis has been found to aid a wide-ranging number of conditions. Demand for it in a medical context is growing due to government recognition. This subsidy has enabled us to expand our small research area and conduct tests on a daily basis. Some such experiments include sonic separation, and various wet and dry methods of sieving. Varieties of cannabis strains and growing methods are also factors to take into consideration. Cannabis strains, their yields and the potency of the resin glands also vary greatly. Lighting conditions also affect glandular trichome size. All these factors must be taken into consideration when assessing techniques of resin gland collection. Microscopy, laboratory tests, chromatography and several other methods of examination should always be employed to assess the true condition of hashish (Figure 4).

Hashish is a considerably easier substance to distribute than herbal cannabis. Storage, longevity, and consistency are all extremely important factors for medical patients who would have to administer it in precise quantities. Herbal cannabis may have little consistency in active components. Cropped buds of the cannabis plant contain varying amount of stalks, leaves and other plant material that have no beneficial therapeutic properties, and may be harmful when smoked. Moreover, as the resin glands coat the buds, heavy handling or pruning can knock off the active trichomes, diminishing potency. Once pressed, hashish is concentrated and compact, easy to store and simpler to divide into measurable doses. As many patients using "medical marijuana" require long-term treatment where

FIGURE 3. Processed "water hash" after Ice-O-Lator® treatment.

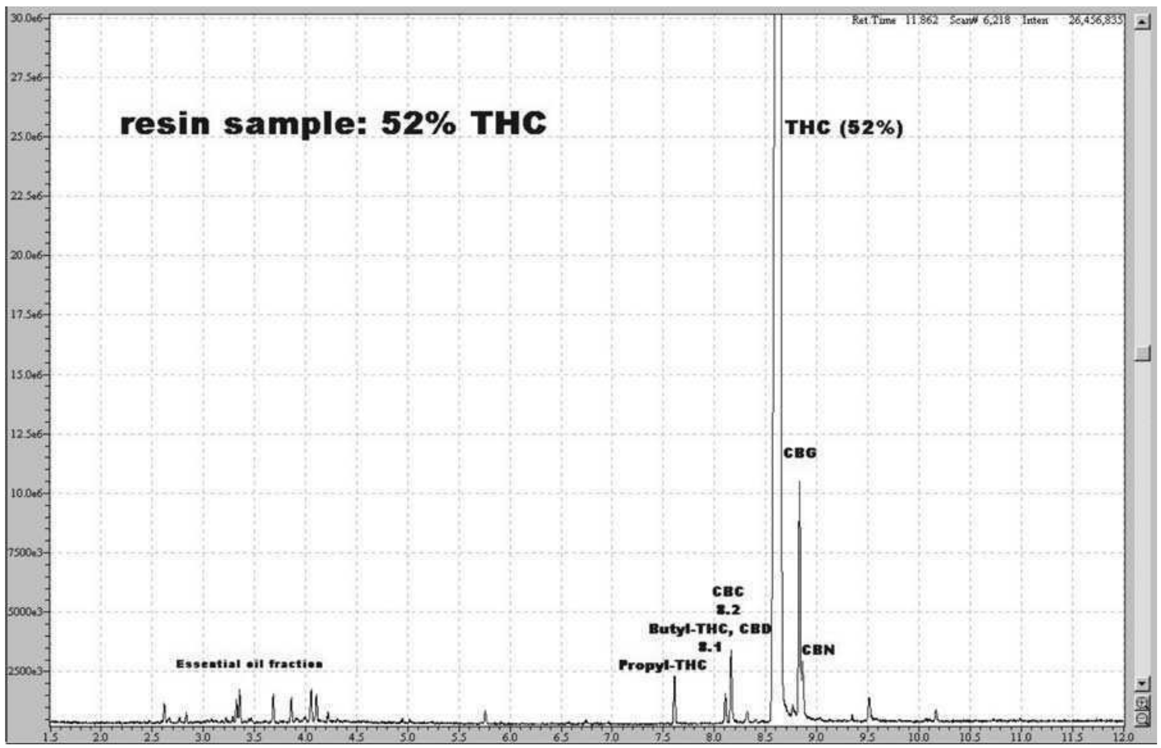


variations in dosage are important, hashish represents a considerably more practical therapeutic product.

For a number of years, both the Ice-O-Lator and Pollinator products have been used to create very pure and potent hashish from drug strains of cannabis. Recently we have begun working using hemp strains of cannabis, which have very low levels of THC and very high levels of CBD. The resulting hashish product is very useful to laboratories that are involved in the synthesis of THC from CBD (Gould 2001), a process described by Gold (1973). By using these products, pre-processing of plant material is easily achieved, ensuring that the laboratories have the best possible plant material to employ, as they may utilize only the resin glands instead of whole plants. As the laboratory work is very expensive, there are huge potential cost-saving benefits in ensuring total efficiency in all aspects of the production. This is of great interest to me, as I feel that hashish is a powerful medicine that has helped many people in cultures all over the world for hundreds of years. I am very happy to be involved in the production of medicines that can help many people.

At the Pollinator Company in spring 2002 there is much activity, as the level of interest in our products has enabled us to expand our shop space while also al-

FIGURE 4. GC/MS of a random Ice-O-Lator® hashish sample (performed by Thomas Herkenroth, THC Pharm, Frankfurt, Germany).



lowing the space to set up a dedicated research and development area. Issues concerning processing methods and medical issues will be discussed and addressed in our ongoing research of medicinal hashish production and its subsequent uses.

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Combined Treatment of Tourette Syndrome with Δ^9-THC and Dopamine Receptor Antagonists

Kirsten R. Müller-Vahl
Udo Schneider
Hinderk M. Emrich

SUMMARY. Animal studies suggest that cannabinoid receptor agonists might enhance the effect of dopamine receptor antagonists (neuroleptics, NL) in hyperkinetic movement disorders. In Tourette syndrome, NL are the most effective drugs for the treatment of tics. Recent clinical trials demonstrated that delta-9-tetrahydrocannabinol (Δ^9-THC) also produces a tic-suppressing effect. In this single case study in a 24 years old female suffering from TS with extreme tics, it is suggested for the first time that Δ^9-THC may be useful in augmenting the pharmacological response to atypical NL such as amisulpride and risperidone in TS patients. No serious adverse reactions occurred. Controlled studies are necessary to confirm this initial report. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@ haworthpressinc.com> Website: <http://www.HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

Kirsten R. Müller-Vahl, MD, Udo Schneider, MD, and Hinderk M. Emrich, MD, are affiliated with the Department of Clinical Psychiatry and Psychotherapy, Medical School Hannover, Germany.

Address correspondence to: Dr. Kirsten R. Müller-Vahl, Department of Clinical Psychiatry and Psychotherapy, Medical School Hannover, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany (E-mail: mueller-vahl.kirsten@mh-hannover.de).

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KEYWORDS. Tourette syndrome, tics, cannabis, THC, amisulpride, neuroleptics

INTRODUCTION

Tourette syndrome (TS) is a chronic neuropsychiatric spectrum disorder characterized by multiple motor and one or more vocal tics. The pathology is still unknown but there is evidence for an involvement of the dopaminergic system (Singer 1997). Dopamine blocking drugs (neuroleptics, NL) are considered the first-line pharmacotherapy for tics. However, these drugs are not effective in all patients, and their usage is limited due to dose dependent side effects such as sedation, weight gain, depression, and irritability (Kurlan 2001).

From animal studies carried out over many years, it is well known that cannabinoids influence motor behavior. It has been demonstrated that acute administration of cannabinoid receptor agonists induces catalepsy and immobility and attenuates turning behavior (Pertwee and Wickens 1991, Souilhac et al. 1995). Central CB_1 cannabinoid receptors are found at very high density in neurons of the basal ganglia. Therefore, there is considerable evidence that cannabinoids modulate the outflow of information from the basal ganglia.

To date the physiological role of the central cannabinoid receptor system is not well understood. However, there is evidence that cannabinoids might be of therapeutic value in different neurological movement disorders. Single case studies and an open uncontrolled trial in five patients suffering from focal and generalized dystonia suggested that cannabidiol (CBD), a non-psychoactive ingredient of *Cannabis sativa*, might be effective in the treatment of different forms of dystonia (Snider and Consroe 1984, Sandyk et al. 1986, Consroe et al. 1986). A pilot study in seven patients suffering from Parkinson's disease (PD) demonstrated that the cannabinoid receptor agonist nabilone reduces levodopa-induced dyskinesia (Sieradzan et al. 2001). In patients suffering from multiple sclerosis (MS) there is evidence that both smoked cannabis and oral delta-9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of cannabis sativa, improves tremor (Consroe et al. 1997, Clifford 1983, Meinck et al. 1989).

In TS, anecdotal reports as well as two randomized double-blind placebo-controlled clinical trials in 12 and 24 patients, respectively, demonstrated that cannabis and Δ^9-THC reduce motor and vocal tics (Sandyk and Awerbuch 1988, Hemming and Yellowlees 1993, Müller-Vahl et al. 1998, Müller-Vahl et al. 1999, Müller-Vahl et al. 2001, Müller-Vahl et al. in press). Several years ago, Moss et al. (1989) suggested that in TS, cannabinoid receptor agonists might enhance the effect of NL in the treatment of tics because animal studies had demonstrated that cannabinoids like Δ^9-THC increase NL-induced hypokinesia (Moss et al. 1984).

In this open uncontrolled single case study in a 24 years old female with TS, we report a successful treatment of motor and vocal tics with a combination of oral Δ^9-THC and amisulpride, an atypical dopamine receptor antagonist.

CASE STUDY

Ms. R. is a 24-year-old female suffering from TS. Motor and vocal tics started at age 9. At the age of 16 years, her clinical status deteriorated and medical treatment was initiated. Between age 16 and 21 several drugs had been prescribed, but either failed to improve tics or could not be tolerated due to significant side effects. The following drugs were used in monotherapy or combination: tiapride, pimozide, sulpiride, olanzapine, clonazepam, fluvoxamine, and clomipramine. At age 21, treatment with risperidone was started and tics improved. Although she complained of side effects such as acute dyskinesia (that required long-term treatment with biperiden), galactorrhea, and amenorrhea, she continued medication. However, by age of 23 years tics worsened again, and could no longer be controlled by risperidone even after the dosage was increased up to 8 mg/d.

At that time, she participated in a randomized double-blind placebo-controlled clinical trial investigating the effect of Δ^9-THC in TS over a 6-week period at our clinic. During the treatment period her tics clearly improved, and then deteriorated after study medication was stopped. During the course of the study, her treatment with risperidone remained unchanged. After completion of the study it turned out that she had received Δ^9-THC (10 mg/d). Therefore, she asked for a prescription of Δ^9-THC for long-term treatment. Unfortunately, her health insurance refused to cover the costs because in Germany Δ^9-THC is not approved for the treatment of TS.

This open uncontrolled study was carried out to reexamine the effect of oral Δ^9-THC in combination with an atypical NL. Tics were rated using examiner rating scales (Global Clinical Impression Scale (GCIS) (Leckman et al. 1988), Shapiro Tourette-Syndrome Severity Scale (STSS) (Shapiro et al. 1988), Yale Global Tic Severity Scale (YGTSS) (Harcherik et al. 1984) and a self-rating (Tourette-Syndrome Symptom List) (TSSL) (Leckman et al. 1988). Using the TSSL the patient was asked to rate not only tics, but also "premonitory experiences" prior to the occurrence of tics.

Baseline visit 1 was performed on monotherapy with 8 mg risperidone. At that time, she suffered from extreme vocal tics, including very loud and frequent yelling and severe coprolalia (compulsive swearing). In addition, she had moderate to severe motor tics with facial grimacing, head jerking, arm extension, jumping, and stamping feet. (For tic rating at visit 1 see Table 1 and Figure 1.)

In the first part of the study, combined treatment with risperidone (8 mg/d) and Δ^9-THC (up to 17.5 mg/d) was started. At a dose of 10 mg Δ^9-THC, tics clearly

improved. Further dose increases, however, did not cause an additional improvement. Tic rating at visit 2 (week 6) was performed at a dose of 17.5 mg/d Δ^9-THC in combination with 8 mg/d risperidone (Table 1, Figure 1). The only reported adverse effect was a mild "high-feeling." Two weeks later, the patient herself reduced the dosage of risperidone at home, but felt that tics deteriorated and, therefore, resumed taking 8 mg/d.

After a treatment period of about 2 months with a combination of risperidone (8 mg/d) and Δ^9-THC (10 mg/d), tics slightly increased. Tic rating at visit 3 (week 12) documented that tics worsened, but did not reach the severity measured at baseline visit 1 (Table 1, Figure 1).

Therefore, treatment with risperidone was stopped and therapy with amisulpride, an atypical neuroleptic drug, was started. Treatment with Δ^9-THC (10 mg/d) was continued. The dose of amisulpride was slowly increased up to 600 mg twice a day. Tics improved in frequency and intensity (visit 4, week 17, for tic rating see Table 1 and Figure 1). The only side effect that occurred was minimal galactorrhea.

To exclude that this improvement was attributable only to the treatment with amisulpride and not to the combination of both drugs, treatment with Δ^9-THC was reduced and discontinued. Tics deteriorated after withdrawal from Δ^9-THC (visit 5, week 19, Table 1, Figure 1) and improved again after resumption of Δ^9-THC (10 mg/d) (visit 6, week 20, Table 1, Figure 1).

One month later a final visit (visit 7, week 24, Table 1, Figure 1) was performed. The patient reported mild tic deterioration compared to visit 6, but still

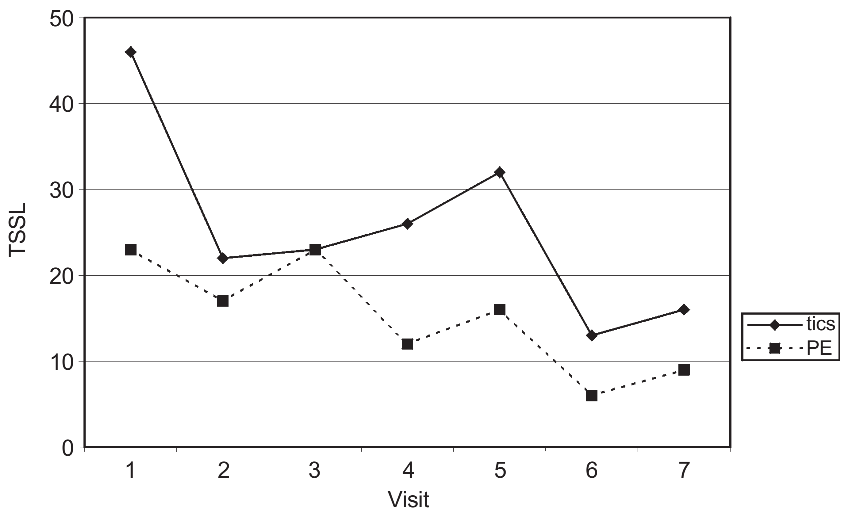
TABLE 1. Tic Rating at Visits 1-7

	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7
GCIS	5	4	5	4	4	4	4
STSS	5	4	5	4	4	3	4
YGTSS	81	67	74	64	70	46	59
TSSL	46	22	23	26	32	13	16
PE	23	17	23	12	16	6	9

GCIS = Global Clinical Impression Scale, STSS = Shapiro Tourette-Syndrome Severity Scale, YGTSS = Yale Global Tic Severity Scale, TSSL = Tourette-Syndrome Symptom List, PE = premonitory experiences (measured by the TSSL).

Visit 1: risperidone (8 mg) monotherapy, visit 2: combination of risperidone (8 mg) and Δ^9-THC (17.5 mg), visit 3: combination of risperidone (8 mg) and Δ^9-THC (10 mg), visit 4: combination of amisulpride (800 mg) and Δ^9-THC (10 mg), visit 5: amisulpride (1200 mg) monotherapy, visit 6: combination of amisulpride (1200 mg) and Δ^9-THC (10 mg), visit 7: combination of amisulpride (1200 mg) and Δ^9-THC (10 mg).

FIGURE 1. Self rating of tics and premonitory experiences (PE) using the Tourette-Syndrome Symptom List (TSSL). Visit 1: risperidone (8 mg) monotherapy, visit 2: combination of risperidone (8 mg) and Δ^9-THC (17.5 mg), visit 3: combination of risperidone (8 mg) and Δ^9-THC (10 mg), visit 4: combination of amisulpride (800 mg) and Δ^9-THC (10 mg), visit 5: amisulpride (1200 mg) monotherapy, visit 6: combination of amisulpride (1200 mg) and Δ^9-THC (10 mg), visit 7: combination of amisulpride (1200 mg) and Δ^9-THC (10 mg).



felt an improvement of motor tics in frequency and intensity and of extreme vocal tics, particularly with respect to their frequency.

Rating of "premonitory experiences" prior to the occurrence of a tic showed that the patient felt that in parallel with the tic improvement, there was a concomitant reduction in the urge to tic especially during combined treatment with Δ^9-THC and amisulpride (Table 1, Figure 1).

DISCUSSION

Anecdotal reports and two controlled clinical trials have suggested that Δ^9-THC is effective in the treatment of tics in TS (Sandyk and Awerbuch 1988, Hemming and Yellowlees 1993, Müller-Vahl et al. 1998, Müller-Vahl et al. 1999, Müller-Vahl et al. 2001, Müller-Vahl et al. in press). Although various other drugs have been found to be useful in the treatment of tics, at present there is general agreement that classic and atypical NL are the most effective anti-tic agents (Kurlan 2001). In this single case study, we report for the first time a suc-

cessful treatment of tics with a combination of Δ^9-THC and the atypical NL amisulpride.

The patient suffered from extreme vocal tics in severe intensity, complexity, and frequency and moderate motor tics. Combined treatment with Δ^9-THC and amisulpride did not eliminate all the tics, but frequency of vocal tics decreased and motor tics improved significantly. A combination of Δ^9-THC and amisulpride was superior compared to a combination of Δ^9-THC and risperidone. Amisulpride was most effective at a high dose of 1200 mg/d, Δ^9-THC at a low dose of 10 mg/d. The only side effect was minimal galactorrhea.

Single case reports are always of limited meaning. However, this patient was followed for more than 6 months. Tics improved after medication was started, deteriorated after withdrawal from Δ^9-THC and improved again after continuation of combined treatment. A positive treatment effect could be observed using both global and complex measures, self and examiner rating scales. The patient herself noted not only a marked tic reduction but also an improvement of premonitory experiences prior to the occurrence of tics. One year before in this patient a comparable beneficial effect of Δ^9-THC had been observed when participating in our double-blind placebo-controlled study. It is worthy of note that the patient desired that no deterioration would occur after withdrawal from Δ^9-THC because a long-term treatment with Δ^9-THC was not possible. Her health insurance refused to cover the costs. She herself could not meet them, and, furthermore, declined to use illegal cannabis.

From these preliminary results, therefore, it is suggested that Δ^9-THC may augment the anti-tic effect of atypical NL such as risperidone and amisulpride. To the best of our knowledge, there is only one single report available suggesting a beneficial effect of amisulpride in TS (Trillet et al. 1990). To date, the neurobiology of TS is unknown. Most evidence, however, supports an active role of the dopaminergic system. It has been suggested that TS is due to dopaminergic hyperinnervation in the striatum or supersensitive postsynaptic dopamine receptors (Singer 1997). It has also been speculated that abnormalities within several neurotransmitter systems (including gamma-aminobutyric acid (GABA), acetylcholine, serotonin, opiates) contribute to TS pathology. Since it has been demonstrated that cannabinoids are effective in the treatment of tics, it can be speculated that the central cannabinoid receptor system might be involved in TS pathology as well (Müller-Vahl et al. in press).

In reserpine-treated rats, an animal model of PD, it has been demonstrated that Δ^9-THC increases hypokinesia (Moss et al. 1981). Another study has shown that hypokinesia induced by the dopamine receptor antagonist haloperidol significantly increase after co-administration of Δ^9-THC (Moss et al. 1984). It, therefore, has been suggested that cannabinoids in combination with NL might be of therapeutic value in hyperkinetic movement disorders such as TS (Moss et al. 1989).

Interpreting these data, different hypotheses can be advanced. The beneficial effect of a combination of NL and Δ^9-THC may be due to an interaction between cannabinoid and the dopaminergic system. Dopamine D1 and D2 receptors both are co-localized with CB_1 receptors in various combinations on the cell bodies and terminal axons of striatal efferent neurons projecting to globus pallidus lateralis (GPl), globus pallidus medialis (GPm), and substantia nigra (SN) (Glass et al. 2000). Several animal studies have demonstrated a highly complex interaction between these two systems within the basal ganglia (Navarro et al. 1993, Giuffrida et al. 1999). Dopaminergic and cannabinoid receptors are both located in the outflow nuclei of the basal ganglia. Therefore, there may be an interrelation of these receptors in the regulation of motor activity (Giuffrida et al. 1999). Repeated stimulation of D1 (but not D2) dopamine receptors enhances catalepsy induced by a potent cannabinoid receptor agonist (Rodriguez de Fonseca et al. 1994). Cannabinoid receptor stimulation attenuates rotational behavior induced by a dopamine D1 (but not a D2) agonist with unilateral lesions of the dopaminergic nigrostriatal pathway (Anderson et al. 1995). Turning behavior induced by cannabinoid agonists can be blocked by D1 and D2 receptor antagonists (Souilhac et al. 1995). In the reserpine-treated rat model of PD it could be demonstrated that cannabinoid receptor agonists reduce D2 (but not D1) dopamine receptor-mediated alleviation of akinesia (Maneuf et al. 1997). Local administration of a D2-like (but not a D1-like) receptor agonist resulted in an eightfold increase of the endogenous cannabinoid release in the dorsal striatum (Giuffrida et al. 1999). Therefore, it has been suggested that the CB_1 receptor system acts as an inhibitory feedback mechanism countering dopamine-induced facilitation of motor activity (Giuffrida et al. 1999).

On the other hand it has been demonstrated that cannabinoids enhance GABAergic transmission in the GPl (Maneuf et al. 1996) and, therefore, enhance inhibitory motor effects resulting in reduced voluntary movements and Parkinson-like symptoms (Wickens and Pertwee 1995). Cannabinoid receptors are located at high concentrations on GABAergic terminals projecting from the striatum to the globus pallidus (GP) and substantia nigra pars reticulata (SNr) (Herkenham et al. 1990). GABA is the major (inhibitory) transmitter in these two motor striatopallidal pathways ("direct" and "indirect" pathway). This circuit is modulated by dopaminergic inputs from substantia nigra pars compacta (SNc), cholinergic striatal interneurons, and serotonergic projections. In PD it has been speculated that cannabinoid agonists such as nabilone reduce levodopa-induced dyskinesia due to an increased GABA transmission in the GPl (Sieradzan et al. 2001).

The distribution of neurotransmitters within the basal ganglia circuits makes different hypotheses possible to explain tic reduction after treatment with a combination of Δ^9-THC and NL. It can be speculated that in TS, Δ^9-THC enhances GABA transmission in the GPl resulting in a reduction of basal ganglia motor

output. On the other hand one might hypothesize that cannabinoids reduce tics by a functional interaction between the dopaminergic and the cannabinoid receptor system within the striatum. However, as long as TS pathology and the role of the central cannabinoid receptor system in this disease both are unknown, only speculation is possible.

In conclusion, from this single case it is suggested that the atypical NL amisulpride is effective in the treatment of tics in TS. Furthermore, there is evidence that this anti-tic effect can be augmented by additional treatment with Δ^9-THC. Previous reports about successful treatment of TS with cannabinoids predominantly included males, because there is higher disease prevalence in male than in female subjects (3-4:1). This study, therefore, suggests that cannabinoids are effective not only in males but also in females suffering from TS.

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Personal Account of Medical Use of Cannabis

Clare Hodges

SUMMARY. The author provides a personal account of her sojourn with multiple sclerosis and its treatment with smoked and oral preparations of cannabis.

Additional information is provided as to the effects, dosing and delivery of cannabis employed by 250 members of the Alliance for Cannabis Therapeutics. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc. com> Website: <http://www.HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Cannabis, medical marijuana, multiple sclerosis, patient advocacy

I discovered I had multiple sclerosis (MS) 18 years ago when I was 25 years old. For several years I was only mildly affected. I carried on working as a television producer, married and had two children. Slowly my condition became worse, so that now I am constantly uncomfortable and tired. I am visually impaired and cannot sleep, eat or move very well.

Multiple sclerosis (MS) is a cruel disease. It develops when you're young and healthy, and slowly but surely you lose all your faculties, abilities and functions.

Clare Hodges, MA, is affiliated with the Alliance for Cannabis Therapeutics, P.O. Box CR14, Leeds LS7 4XF, England (E-mail: clare@dallases.free-online.co.uk).

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Nowadays you can often expect to live your full life span until you become completely dependent, and of course this is a very depressing prospect. I began to get gloomy and introspective, as all my future seemed to hold was deteriorating health, since I had not found any medicines that really helped.

The medicines prescribed only gave limited relief and often with unacceptable side effects. Over the years I've been given steroids, tranquilisers, painkillers, muscle relaxants and antidepressants. At best they only helped in the short term, and many have intolerable side effects. My main problem, however, was that my bladder was in constant spasm and no prescribed medicines helped me. For several months I took oxybutinin to help my bladder. This didn't help the problem, but I persevered, hoping at some time it might. However, it gave me side effects of blurred vision and headaches. My nights were so disturbed by the bladder problems, I was given temazepam to help me sleep, which did get me off to sleep, but left me slow and 'hung-over' the following day. Using cannabis helped me gradually cut back on these medicines, so that I stopped oxybutinin, and cut down on temazepam. I much preferred using cannabis because not only did it seem just as effective, but also I felt I had control over my medication, which was very important.

In 1992 I read an article in a U.S. journal about how some doctors had observed cannabis could help people with MS. Before I did anything I talked to different doctors I saw. None of them knew much about it, but said they thought it wouldn't do me much harm in moderate quantities, and indeed it was probably safer than many of the medicines they could prescribe.

As I was a middle class mother of two very young children I had a bit of a problem obtaining cannabis. My life revolved around the local mothers and toddlers group and it was sometimes quite embarrassing asking people if they could assist me, but eventually I found someone who did help me get some and showed me how to use it. I had approached a woman I knew from when I was working who I'd been told used cannabis. I didn't know her very well, but decided to ask her for help. Like most people, she was happy to help someone in trouble, and came around one evening when the children were in bed. She brought some cannabis, tobacco and papers, and showed me how to roll a joint. She smoked some with me, talking me through what I might be experiencing, constantly telling me to take it slowly. I'd tried cannabis about twice when I was a student, but without much effect, so I was very naïve. I had smoked cigarettes for a few years when I was younger, and still have an occasional cigarette, so smoking tobacco was familiar to me. The advice she gave to go slowly was very good, as I now know it is easy to take too much if you're not careful.

When I did try cannabis, the physical relief was almost immediate. The tension in my spine and bladder was eased, and I slept well. I was comfortable with my body for the first time in years. Just as important, I felt happy that there was

something, after all, that could help me. It was as if a huge weight had been lifted from me.

My MS symptoms vary considerably. Sometimes I can appear very well, and at other times I look and sound very handicapped. Similarly, I can be cheerful about my situation, but when the MS is bad I become very introspective and gloomy. Very simple tasks take enormous effort and leave me exhausted. Cannabis helps to stabilize my health and I find I can now do simple things that I hadn't been able to do, like go to the shops, or cook my children's dinner after school.

It took a couple of months to work out how to self-medicate. The main problem, which continues to this day, is working out how to use each new batch as strength and quality differ considerably. To begin with, it was easy to take too much or too little. If I took too much I became uncoordinated and confused, which distressed me and made it harder to deal with the condition. I have now established a routine that helps. I take 9 grams of herbal cannabis per week, drinking it in milky drinks during the day, and smoking it at night before I go to bed. To make the drink, I simmer the cannabis in milk for a few minutes, sieve the milk to remove the leaves, then drink the milk. I do not smoke it with tobacco, but dried herbs in a herbal tobacco mix you can buy in health food shops. I've found smoking is the easiest way of taking it to treat my disease, as it is much easier to regulate the dose. MS is a particularly unpredictable disease, not just in the long term, but from day to day, and almost hour to hour. Over 24 hours I would usually expect to take 4 joints (half cannabis, half herbal tobacco). However, the total number can be only two, or up to six or seven, depending on the state of health.

So, it's vitally important that MS patients have some kind of control over when and how much of the medicine they take, in the same way that patients often self-titrate for pain relief.

There was concern expressed by politicians and charities when medical use of cannabis was first talked about, that patients would become addicted to cannabis and would be tempted to take 'harder' drugs. I've never been able to take this very seriously, but I thought I'd say that I don't feel in any way addicted to cannabis. If for some reason I can't use it (such as when travelling abroad), I don't crave it or suffer withdrawal symptoms; the MS simply gets worse.

I've been prescribed nabilone, the only available cannabinoid preparation currently available in Britain. I took 1 mg daily for four nights, but it made me confused and clumsy. I persevered for four days, hoping it might be a substitute, but it wasn't. It's not clear to me whether a synthetic preparation will ever have the same therapeutic benefit as the natural plant.

My neurologist was very impressed by how much better I was. He put me in touch with two other patients with MS who also used cannabis. When we found out that cannabis in tincture form was available by medical prescription in Britain until 1973, we decided to start an organisation based on the U.S. Alliance for Cannabis Therapeutics (ACT) to press for cannabis to be moved from Schedule 1

to Schedule 2 and thereby restore it as a legal medicine. It has involved an enormous amount of work, dealing with thousands of letters from patients, doctors and politicians. The ACT has never pressed for legalisation of cannabis and has no 'hidden agenda.' I've always thought a great strength of our group is that it's been run and financed entirely by patients. We do not fund-raise nor have we applied for charitable status, but have remained quite independent. It was doubtless thanks to our independent status that official bodies have regularly consulted the ACT.

We were very involved in the British Medical Association report and were interviewed by the House of Lords Select Committee on cannabis. Led by Austin Mitchell, MP, we took two delegations of patients and doctors to talk to the Ministers of Health and the Home Office. These delegations were very distinguished, including Lord Whaddon, who suffers from MS, and Professor Patrick Wall, the specialist in pain control.

In 1997 we invited the director of a pharmaceutical company, GW Pharmaceuticals, to join our delegation when the doctors and politicians representing the ACT asked the Department of Health Minister, Paul Boateng, if his company could be granted a licence to grow cannabis for medical research. This was issued shortly afterwards and clinical trials are now proceeding with a preparation manufactured by the company and administered via a sublingual spray. Following this, the Medical Research Council has set up several trials around the country, using synthetic versions of cannabis.

I've been using cannabis for nine years. There is no doubt that my condition has improved in different ways. I do not have to take as many prescribed medicines. I now eat better, sleep better, and I feel more positive and motivated.

GENERAL OBSERVATIONS FROM PATIENTS

I've outlined my personal experience of using cannabis with MS, but I'm also in a position where I can give a broader overview as over the last nine years I've talked to or corresponded with many patients who use cannabis. Of the 3,000 letters the ACT has received, there are about 250 patients who have written about their use of cannabis in some detail. There have been more letters from women than men, and they have tended to be older rather than younger. I assume this reflects the general pattern of people with MS. Although most women are early or late middle-aged, a handful of much older people (70+) have also written about their experiences. Several of these I have followed up by visiting and talking to the people who wrote in.

Here are some thoughts I now want to pass based on these letters and conversations over the years.

PSYCHOACTIVITY

There is a recurring theme through all the letters patients write: cannabis helps them because it not only eases their physical problems, but also improves their mood, lifts their spirits, and gives them a better quality of life.

There's a large literature about the effects of cannabis, but when you're chronically ill your experience of all these effects is somewhat different.

Like all medicines and drugs cannabis has a mixture of physical and psychoactive effects. One common physical effect is that it relaxes muscles, which is one reason why people enjoy using it, but when you have MS relaxing muscles is not just fun–it is very important. For many of us it takes much effort and concentration just to move around and do ordinary things. I know this makes me slightly tense all the time which is very wearing and uncomfortable and can result in going into spasm. So relaxing muscles is not just a way of 'chilling out,' but can mean people are able to function more normally.

Similarly, the more I talk to ill and disabled people who use cannabis, the more I think the psychoactive effects are vital to its therapeutic value. There's been great interest in developing drugs that will affect the physical progress of the disease, but for many sufferers and their families being depressed and demoralised is the hardest aspect of the disease to live with and can be extremely debilitating. In the same way that your physical strength diminishes, your mental powers and spirit weaken. One person who wrote to our group put the benefits of the psychoactive effects very well. He said that "people in good health who smoke cannabis get high, while if you've got MS, you're under par all the time, you don't move properly, see properly, have much energy, and cannabis lifts you to normality."

It has been slightly disheartening when some people say we need to find a version of cannabis without the psychoactive effects. This could only work well for a type of MS that produces no psychological effects. The effort to eliminate mood-altering effects seems to me to be a fundamental misunderstanding of how it helps us.

DELIVERY METHODS

Most people choose to smoke cannabis, for the reasons I've mentioned, but many don't like smoking. I've been very impressed by how inventive people are about how to take the cannabis. Two of the people I went to see in the Orkney Islands have developed a skin patch. They simply put some home-grown cannabis on their skin and cover with cling film and a surgical waterproof bandage. They say this gives them a regular, low dose of cannabis that keeps them going for a couple of days. Several people bake it in cakes, but often have a problem as they don't know how it is distributed. I went to see a lady in my home county, Yorkshire, who has got around this by baking little buns with just a tiny pinch in each

bun. This simple, neat solution really appealed to me. Someone else has tried to use it as a suppository, but seemed very primitive. This lady with MS did not continue with the suppositories, finding smoking much easier, if more wasteful.

DOSAGE

It is remarkable the very different amounts people use to find relief. For some, an ounce of herbal cannabis may last four months, for others only two weeks. Similarly the amount used can vary considerably in the same patient. Research could be more flexible in amounts tested on patients, acknowledging the unpredictability of the disease.

In general, patients who use cannabis now outside the law are a rich source of information. Their experiences could help direct any further research.

Cannabis in Multiple Sclerosis: Women's Health Concerns

Denis J. Petro

SUMMARY. Women's health has received greater attention with the recognition of significant differences in disease expression and drug action in men and women. Multiple sclerosis is a neurological disorder with important gender differences. MS patients have employed cannabis to treat a number of symptoms associated with the disease including spasticity, pain, tremor, fatigue, and autonomic dysfunction. The scientific literature includes supportive case reports, single-patient (N-of-1) trials and randomized clinical trials. Large-scale clinical trials are underway to answer questions concerning the efficacy and safety of cannabis in patients with MS. While these studies will answer important questions concerning the actions of cannabinoids on the nervous system, additional studies in female MS patients will be needed to address issues such as gender-specific actions on symptoms such as pain and autonomic dysfunction along with studies in menopausal and post-menopausal women. Since the drug-drug interactions have been reported with cannabinoids, the effects of cannabis on the actions of other centrally-acting drugs should be explored.

KEYWORDS. Multiple sclerosis, cannabis, cannabinoids, spasticity, women's medicine

Denis J. Petro, MD, 1550 Clarendon Boulevard, Suite 510, Arlington, VA 22209-2783 (E-mail: djpmsmd@aol.com).

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INTRODUCTION

Women's health issues have received attention as gender differences in disease expression and drug action are discovered. A gender-based approach recognizes the fundamental physiologic differences between men and women. The areas of difference between men and women in the nervous system are extensive including anatomy, cell numbers, neurotransmitter systems, response to hormones, sensation threshold and disease frequencies. Gender and multiple sclerosis (MS) has been the subject of several excellent reviews (Olek and Khoury 2000; Coyle 2000). Specific disorders such as migraine headache, depression and motor neuron disease also show clear gender preferences.

Multiple sclerosis is a disorder with important gender-associated differences in expression. Cannabis also interacts with the endocrine and immune systems of males and females with distinctions. As therapeutic cannabis use among MS patients has increased over the past generation, a review of the subject with attention to women's health concerns is warranted.

Multiple sclerosis is the most common cause of chronic neurological disability in young adults (Rusk and Plum 1998), and is more likely seen in women and in those who grew up in northern latitudes. In a summary of 30 incidence/prevalence studies, the cumulative female-to-male ratio was 1.77:1.00 (Irizarry 1997). With 350,000 MS patients in the United States, the number of female MS patients is approximately 225,000. Gender is clearly a determinant of susceptibility to MS. The increased female incidence in MS is similar to other autoimmune diseases with onset of symptoms in adulthood such as myasthenia gravis, Hashimoto's thyroiditis, Sjögren's syndrome and systemic lupus erythematosus. The female preponderance in MS lessens in those in whom presentation occurs later in life. MS attacks are less frequent during pregnancy while the postpartum period is one of higher risk (Whitaker 1998). While the postpartum increase in risk for MS attacks may discourage childbearing, women who have borne a child fare better in the long term than those women who have not (Runmarker and Anderson 1995). Interestingly, the occurrence of a first pregnancy may lead to some permanent change in immune status.

Recognizing that current MS treatment is less than optimal, the use of cannabis offers an opportunity to demonstrate the therapeutic potential of cannabinoids on a number of neurological symptoms. In a survey of health care in 471 people with MS in the United Kingdom, use of cannabis was acknowledged by 8% (Somerset et al. 2001). Extrapolating to the 60,000 MS patients in the UK provides an estimate of 4,800 MS patients who employ cannabis in the UK and 28,000 in the United States. In a publication commenting on the use of cannabis in South Africa, James (1994) reported the experiences of a female MS patient (p. 369):

> A few years ago I had started to eat small quantities of marijuana . . . the effects were immediate and remarkable. Control of bladder functioning which was a humiliating problem is restored to normal and has been a liberating influence in my life-style. I can now go out shopping, to the theater, etc., without anticipation of dread and panic. Painful and disturbing attacks of spasticity are relieved and now restful patterns of sleep are ensured where previously sleep was disrupted by urinary frequency or pain and discomfort not least I can laugh and giggle, have marvelous sex and forget that I have this awful, incurable, intractable disease.

The challenge for physicians is to evaluate patient observations using scientific methodology. Many authors have described individual patient experiences of therapeutic use of cannabis to treat symptoms of MS (Grinspoon and Bakalar 1997; Brown 1998; Iversen 2000). Additional support has been provided by single-patient clinical trials (N-of-1) and prospective double-blind placebo-controlled studies.

TREATMENT OPTIONS: ACUTE EPISODES, DISEASE MODIFICATION AND SYMPTOM MANAGEMENT

Management of an acute episode of demyelination in MS is sometimes achieved to a limited extent with corticosteroids. Disease modification is difficult to assess because MS is a chronic, unpredictable disorder in which the burden of white matter involvement is highly variable and the clinical response to drug treatment is modest. Five drugs have been approved by regulatory authorities to modify the clinical course of MS. Avonex® (interferon-beta-1a), Betaseron® (interferon-beta-1b), Copaxone® (glatiramer acetate/copolymer 1), and Rebif® (interferon beta 1a) have demonstrated efficacy in relapsing-remitting MS and may slow the course of secondary progressive MS. Novantrone® (mitoxantrone) is approved for secondary progressive and progressive relapsing MS. Immunosuppressants such as corticosteroids, methotrexate, and cyclophosphamide have been used to alter the natural history of MS with some success.

CANNABIS IN ACUTE TREATMENT AND DISEASE MODIFICATION

While patients may claim that cannabis can alter the natural history of MS, no clinical trials have been conducted in either acute treatment or disease modification. Data from animal research supports cannabinoids as a potential disease modifying treatment for MS. The immune-mediated disease, experimental autoimmune encephalomyelitis (EAE), is considered the laboratory model of MS. In

a study in the Lewis rat and guinea pig, Lyman and colleagues (1989) demonstrated that the oral administration of Δ-9-tetrahydrocannabinol (THC) was effective in the prevention and suppression of EAE. The authors suggested that Δ-9-THC might prove to be a new and relatively innocuous agent for the treatment of immune-mediated diseases such as MS. Since Δ-9-THC is the cannabinoid associated with negative psychotropic actions, investigators used other cannabinoids to assess actions in EAE. Wirguin and colleagues (1994) studied the effect of Δ-8-THC on EAE in the rat. Orally administered Δ-8 THC significantly reduced the incidence and severity of neurological deficit while parenteral administration was not effective. The difference can be explained on first-pass metabolism in the liver, which produces the active metabolite. Additional support for beneficial effects of cannabinoids in EAE was reported by Achiron and co-investigators (2000) using a synthetic non-psychotropic cannabinoid, dexanabinol (HU-211). The authors suggested that dexanabinol may provide an alternate treatment of acute exacerbations of MS. Finally, Guzman, Sanchez and Galve-Roperh (2001) reviewed the experimental evidence showing the protective effects of cannabinoids from toxic insults such a glutamatergic over-stimulation, ischemia and oxidative damage. The authors described the potential of cannabinoids to downregulate inflammatory cytokine production.

If cannabinoid drugs are to be used in acute treatment of MS or in disease modification, then studies in female patients will be needed. These studies involve assessment of drug effects on fertility, pregnancy and in nursing mothers. Since inclusion of women in early clinical trials is usually insufficient to identify gender-based differences in response, animal models are used to identify potential pharmacologic and toxicological effects (Christian 2001). Unfortunately, current animal models do not consistently demonstrate gender-based differences seen in humans. The cannabinoid Δ-9-THC is marketed in the United States as Marinol® and information concerning use in women is provided in the Physicians' Desk Reference (2002). Marinol is included in Category C (FDA designation for drugs with animal data showing harm to the fetus with no controlled human studies). The drug labeling states that Marinol should be used only if the potential benefit justifies the potential risk to the fetus. Likewise, its use in nursing mothers is not recommended since Marinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.

Drug interaction studies would be needed to investigate the potential for significant interactions with drugs commonly used by women. Because cannabinoids are highly bound to plasma proteins and might displace other protein-bound drugs, dosage adjustment for other highly protein-bound drugs may be needed. In addition, drugs metabolized by hepatic mixed-function oxidase enzymes may be inhibited by cannabinoids (Benowitz and Jones 1977). In the PDR drug interaction section for Marinol, specific precautions are in-

cluded regarding potential interactions with a number of drugs including sympathomimetic agents, antihistamines, tricyclic antidepressants, muscle relaxants, barbiturates and theophylline. Other drugs which may be important in female patients include birth control drugs, hormones administered to treat symptoms associated with menopause, steroids, and drugs used in the treatment of osteoporosis.

The effects of inhaled cannabis on fetal development have been studied extensively. In a study of six one-year-old infants exposed daily to cannabis prenatally and through breastfeeding, no malformations were found in cannabis-exposed infants (Tennes et al. 1985). A prospective study of the effects of prenatal exposure to cigarettes and cannabis on growth from birth to adolescence found no significant effects on growth measures at birth although a smaller head circumference observed at all ages reached statistical significance among the adolescents born to heavy marijuana users (Fried et al. 1999). Finally, the relationship between maternal use of cannabis and pregnancy outcome was investigated in a study of 12,000 women in the UK (Fergusson et al. 2002). Five percent of mothers reported smoking cannabis before and/or during pregnancy. The use of cannabis during pregnancy was not associated with increased risk of perinatal mortality or morbidity. The babies of women who used cannabis weekly before and during pregnancy were lighter than those of non-users and had shorter birth lengths and smaller head circumferences. The findings of this study are consistent with earlier studies that have found an absence of statistical association between cannabis use and antenatal or perinatal morbidity and mortality. The reduced birth weight seen with regular or heavy cannabis use suggests that to optimize fetal growth and minimize the risk of an adverse pregnancy outcome, pregnant women should limit cannabis use during pregnancy. In female patients during the reproductive years, fertility and pregnancy are usually not affected by MS. While MS activity seems to decrease during pregnancy, exacerbation rates increase in the first 6 months postpartum (Birk and Rudick 1986). Since cannabinoids are secreted in human breast milk and absorbed by the nursing baby, cannabis use while breast-feeding should be avoided.

Special studies of cannabis in menopausal and post-menopausal women have been conducted. Mendelson and colleagues (1985) studied LH levels in menopausal women after marijuana smoking and found no significant difference in LH levels when compared to values for healthy menopausal women. In a study of the acute effects of marijuana smoking in post-menopausal women, Benedikt and colleagues (1986) noted statistically significant increases in pulse rate, intoxication levels and the confusion component of the Profile of Mood States Questionnaire (POMS). The finding of neuropsychological performance impairment in post-menopausal women is not unlike the findings in moderate cannabis users (Pope et al. 2001) and in heavy cannabis users (Solowij et al. 2002). The degree of impairment in memory and attention are not surprising in chronic heavy users.

Pope (2002) presents the consensus opinion that some cognitive deficits persist for hours or days after acute intoxication with cannabis has subsided. Since cognitive impairment is associated with MS, the potential for significant adverse effect on memory and attention in MS patients using therapeutic cannabis should be a subject of future clinical research.

CANNABIS IN SYMPTOM MANAGEMENT

Manifestations of MS are protean and depend on the location of persistent central nervous system lesions. Since MS lesions have a predilection for certain anatomic locations, recognizable clinical syndromes are common in MS. Surveys of symptoms in MS have been carried out with the most common symptoms including fatigue, balance impairment, muscle disturbances (weakness, stiffness, pain and spasm), and bowel and bladder impairment (Compston 1997). In chronic MS, signs and symptoms of motor dysfunction are found in at least 75 percent of patients (Miller 2000) with sensory impairment noted in 50 percent. Cerebellar abnormalities (ataxia, tremor, nystagmus or dysarthria) are found in at least a third of MS patients. Autonomic symptoms including bowel, bladder or sexual dysfunction are found in at least 50 percent of patients.

A survey of cannabis-using MS patients in the USA and UK by Consroe and colleagues (1997) reported improvements after cannabis use in spasticity, chronic pain, acute paroxysmal phenomena, tremor, emotional dysfunction, anorexia/weight loss, fatigue, diplopia, sexual dysfunction, bowel and bladder dysfunction, vision dimness, dysfunction of walking and balance, and memory loss (descending rank order). While the authors of this study discuss the potential shortcomings of the survey design, this report suggests that cannabis may significantly relieve signs and symptoms of MS such as spasticity and pain along with a number of other complaints.

IMPAIRED MOBILITY: SPASTICITY

In the 19th century, O'Shaughnessy (1842) used hemp extract in treating muscle spasms associated with tetanus and rabies. Reynolds (1890) reported using cannabis to treat muscle spasms, as well as for epilepsy, migraine, and other indications. While medicinal cannabis use continued in the years after the work of O'Shaughnessy and Reynolds, little was published concerning cannabis and spasticity until the 1970s. A survey of 10 spinal-cord injured males was published in 1974 in which 5 patients reported reduced spasticity, 3 patients noted no effect and 2 patients did not have significant spasticity (Dunn and Davis 1974).

The use of cannabis to treat spasticity associated with MS has been reported by a number of investigators over the subsequent interval. Petro (1980) reported

one patient with MS who used cannabis to treat nocturnal leg fatigue and spasms associated with spasticity. Petro and Ellenberger (1981) conducted a double-blind clinical trial that demonstrated statistically significant reduction in spasticity following the oral administration of Δ-9-THC in doses of 5 and 10 mg. Investigators have confirmed the observation using Δ-9-THC (Hanigan et al. 1985; Ungerleider et al. 1988; Maurer et al. 1990), cannabis (Meinck et al. 1989) and nabilone (Martyn et al. 1995). Additional preclinical support for the benefit from cannabis in spasticity was provided by the report of Baker and colleagues (2000). In this study, cannabinoid receptor agonism improved tremor and spasticity in mice with chronic relapsing experimental allergic encephalomyelitis (CREAE) and indicated that the endogenous cannabinoid system may be active in control of spasticity and tremor. Further support for cannabinoid receptor involvement was provided in an animal study in which cannabinoid receptor (CB_1) changes were found in regions of the brain involved in the control of motor symptoms (Berrendero et al. 2001). The role of the endocannabinoid system in spasticity was demonstrated in CREAE mice in a further study, which manipulated tone using cannabinoid receptor agonists and antagonists (Baker et al. 2001).

Since a considerable body of scientific evidence supports the efficacy of cannabinoids in spasticity, review articles (Gracies et al. 1997; Consroe 1999) and medical texts (Compston 1999; Compston 2001) include cannabis as a treatment option in spasticity. In *Brain's Diseases of the Nervous System Eleventh Edition* (Compston 2001), among the treatments for spasticity associated with MS, cannabinoids are listed along with baclofen, dantrium, benzodiazepines and tizanidine.

Gender issues are involved in MS-associated spasticity. Since females are more likely to experience demyelination at an earlier age than males, the burden of white matter disease over time may be greater in females. The earlier appearance of symptoms in females is somewhat counterbalanced by a greater prevalence of spinal MS seen in males and occurring later in life. The late occurring form of MS often involves progressive spinal lesions presenting with spasticity and pain.

TREMOR

Tremor in MS is treated with beta-blockers, anticonvulsants or, in rare cases, stereotactic procedures. Experimental evidence for benefit from cannabis is provided in a preclinical study by Baker and colleagues (2000) in which treatment with a CB_1 antagonist resulted in increased forelimb tremor. Since isolation of tremor from spasticity may be difficult in experimental animals, interpretation of such evidence may be questioned. In the survey of patients with MS by Consroe and associates (1997), 90% of subjects with tremor reported improvement after

cannabis. In a study of 8 MS patients with tremor and ataxia, oral THC was effective in 2 of 8 subjects with both subjective and objective improvement (Clifford 1983).

NYSTAGMUS

Nystagmus is an eye movement abnormality often associated with MS. In an N-of-1 clinical trial, a 52-year-old man with MS and pendular nystagmus was studied in the United Kingdom over 3 months before and after cannabis in the form of cigarettes, nabilone and cannabis oil-containing capsules (Schon et al. 1998). The investigators demonstrated improved visual acuity and suppression of the patient's pendular nystagmus after inhaled cannabis and were able to correlate the therapeutic effect with acute changes in serum cannabinoid levels. Nabilone and orally administered cannabis oil capsules had no effect. Because of the anatomical relationships involved in eye movement control, the authors suggest an effect at the level of the dorsal pontine tegmentum. In support of action at the level of the deep brain stem is the benefit seen with cannabis in intractable hiccups (Gilson and Busalacchi 1998) and evidence supporting cannabinoid analgesic actions mediated in the rostral ventromedial medulla (Meng et al. 1998). Responding to the report of benefit in nystagmus associated with MS, Dell'Osso (2000) reported an individual with congenital nystagmus whose oscillations dampened after smoking cannabis. Dell'Osso commented that while he had seen similar reports from patients, cannabis research is discouraged in the United States.

POSTURAL REGULATION

The complex integration of sensory and motor function required for postural regulation is impaired in many patients with MS. Impairment of posture is most disabling for patients, distressing for caregivers, and frustrating for physicians. Lesions of spinal, cerebral and cerebellar pathways result in loss of balance. In a study of 10 MS patients, inhaled cannabis caused increased postural tracking error both in MS patients and in normal control subjects (Greenberg et al. 1994). The authors admitted in their publication that dynamic posturography "is not a measure of spasticity." Some authors have reported incorrectly that this study is a negative study in spasticity. Since cerebellar dysfunction is a common finding in MS seen in a third to 80 percent of patients, one can anticipate that many MS patients with both motor and cerebellar symptoms may find improved spasticity and impaired balance. Cannabinoids should be used with caution in patients with the combination of corticospinal (spasticity) and cerebellar (balance) deficits.

FATIGUE

Fatigue is one of the most frequently reported symptoms in MS and is clearly distinct from fatigue experienced in an otherwise healthy individual. The mechanism for fatigue in MS is unknown. No differences have been found in the level of MS-associated fatigue between men and women. Clinical trials have demonstrated that amantadine may be beneficial; however, the supporting evidence is weak (Branas et al. 2000). In a single-blind trial of modafinil in patients with MS (Rammohan et al. 2002), fatigue scores were improved during treatment (200 mg/day). In the only study addressing the effect of cannabis on fatigue, Consroe (1997) reported survey data which showed from 60 to 70% of subjects reported cannabis reduced fatigue states (tiredness, leg weakness). No controlled clinical trials of cannabinoids have investigated this condition.

PAIN

Because of the nature of MS as a disruption of transmission of nerve impulses, paroxysmal manifestations are commonly seen including tonic brainstem attacks, trigeminal neuralgia, and spasticity. Anticonvulsants and antidepressants are commonly used in MS pain syndromes, with some benefit. Cannabinoids have not been studied extensively in MS-associated pain. In other pain models, cannabinoids have demonstrated efficacy comparable to potent analgesics, such as the opioids (Campbell et al. 2001). Gender differences can affect pain via biological differences in the nociceptive and perceptual systems. In humans, women are, in general, more sensitive to painful stimuli when compared to men (LeResche 2001). The prevalence of pain syndromes in female patients with MS has not been studied.

BLADDER DYSFUNCTION

Bladder impairment in MS is seen in up to 80% of patients at some time during the course of the disease and can vary from slight inconvenience to potentially life-threatening when renal function is compromised. The complex interaction between bladder detrussor and sphincter function is disrupted with spinal cord lesions in MS. Drugs used in the treatment of spasticity such as baclofen and diazepam are effective in treating bladder symptoms in many MS patients by inhibiting the urethral sphincter. MS patients, as the example of the female patient from South Africa described earlier (James, 1994), report improvements in bladder function after cannabinoid use. Based on the observations of improved urinary tract function, an open-label pilot study of cannabis based medicinal extract (CBME) has been reported by Brady and colleagues (2001). In this study

sublingual CBME improved lower urinary tract function in 10 patients with advanced MS and refractory urinary tract dysfunction over 8 weeks of treatment.

SEXUAL DYSFUNCTION

Treatment of sexual dysfunction in male MS patients includes a range of options including pharmacological treatments such as sildenafil (Viagra®), papaverine or phentolamine. No treatment other than local administration of artificial lubrication is available for treatment of sexual dysfunction in females. In the Consroe survey of cannabis effects on MS signs and symptoms (1997), 51 subjects reported sexual dysfunction with 62.7% claiming improvement in sexual function after cannabis. No analysis by gender was reported. Based on previously reported survey data, the clinical study of cannabis as a treatment of sexual dysfunction in MS appears warranted.

DISCUSSION

Neurologists in practice in the 1970s noted two distinct patient groups using therapeutic cannabis. Military personnel injured in Vietnam claimed that cannabis was helpful in controlling symptoms associated with traumatic spinal injury. Female patients described beneficial effects from cannabis in treating spasticity, migraine headache or menstrual pain. These observations led to a number of small clinical trials supporting the claims of individual patients. Because of regulatory hurdles in conducting clinical research with cannabis, the total number of patients treated with cannabinoid drugs remains low.

Fortunately, interest in the subject has increased with the initiation of several large-scale cannabis studies in MS in the United Kingdom. The National Institute of Clinical Excellence (NICE), the UK regulatory authority, will assess the results of clinical trials scheduled be completed by the end of 2002.

Over the years, many patients have asked questions concerning the efficacy and safety of cannabis as a therapeutic agent. While cannabis remains as a prohibited drug in the United States, Δ-9-THC is marketed as Marinol® without objection. One can contrast a potential package insert for cannabis with that for the antispastic drug, Lioresal® Intrathecal. With the use of Lioresal via a spinal pump, the drug labeling states that in clinical trials "13 deaths occurring among the 438 patients treated with Lioresal Intrathecal in premarketing studies." Interestingly, two MS patients died suddenly within 2 weeks of drug administration. Imagine the regulatory reaction if a single patient would die after cannabis use. A potential risk associated with cannabis is secondary to the inhalation of cannabis containing smoke. The evidence of significant health risk associated with cigarette smoking is overwhelming. While many patients avoid inhalation

risks by using oral cannabis, the rapid action of an inhaled formulation is effective with symptoms such as flexor spasms or tonic brainstem attacks. One study noted an elevated risk of myocardial infarction (4.8 times baseline) in the 60 minutes after cannabis inhalation (Mittleman et al. 2001). While cannabis was considered a rare trigger of acute myocardial infarction, risk elevation was associated with obesity, current cigarette smoking and male gender.

Additional safety concerns associated with cannabis use in MS include the negative effects of cannabis on balance and cognition. While these negative effects may limit the potential usefulness of cannabis as a treatment of chronic symptoms in MS, many MS patients may yet benefit from cannabis.

While the interest in cannabis as a therapeutic agent for MS is high, many unanswered scientific questions remain including:

1. How does cannabis compare with current standard treatments for MS symptoms?
2. Can alternative delivery systems be developed to provide rapid onset of action with greater safety when compared to inhaled cannabis?
3. Can specific cannabinoids be used more effectively to stimulate or block cannabinoid system receptor activity?
4. Can the immune-modulating actions of cannabis be used to alter the natural history of MS?
5. Can the long-term risks and benefits of cannabis be quantified to determine a useful risk/benefit ratio in treating the life-long disability in MS?

CONCLUSIONS

Evidence in support of cannabis treatment for spasticity associated with MS includes animal studies and a small number of clinical trials using cannabinoid drugs. Clinical reports of benefit in tremor and nystagmus have been published in MS patients. Potential other signs and symptoms in MS, which may be improved with cannabis, include fatigue, pain, bladder disturbances and sexual dysfunction. Women are twice as likely as men to develop MS. Gender specific concerns in female patients include use of cannabis during pregnancy, potential effects on the fetus, and risks associated with breast-feeding. Large-scale clinical trials may provide some answers concerning the potential of cannabis in treatment of MS.

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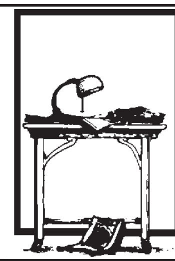
EDITORIAL



It is with great pleasure that the *Journal of Cannabis Therapeutics* initiates its third volume and year of publication. While political controversy concerning clinical cannabis continues, the pace of research quickens, as each month offers new insight in the physiological role of endocannabinoids.

We initiate the new volume with a monumental review of cannabinoid pharmacokinetics by Franjo Grotenhermen. This contribution is most welcome, as he has collected a tremendous amount of useful information and distilled it into a most accessible form that will be a key reference source for scientists and clinicians alike.

Dale Gieringer provides an interesting analysis of the increasing pervasiveness of clinical cannabis usage in the United States. The degree of its acceptance by the public, and the governments of certain states, may come as a surprise to many, and this paper is certain to provoke political controversy as it challenges the conceptual basis of cannabis as a Schedule I drug with no accepted medical usage.

Finally, Markus Storz of Vapormed, Tuttlingen, Germany, has been kind enough to perform an e-mail interview (with minimal editorial changes) to address some of the technical aspects of cannabis vaporization. Vaporization technology represents an increasingly prevalent technique for the application of clinical cannabis. The biophysics and

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rationale for its use provide interesting insights into how this method of cannabis usage may provide harm reduction and obviate the need for clinical patients to smoke their medicine.

Ethan Russo, MD
Editor

Clinical Pharmacokinetics of Cannabinoids

Franjo Grotenhermen

ABSTRACT. Absorption and metabolism of tetrahydrocannabinol (THC) vary as a function of route of administration. Pulmonary assimilation of inhaled THC causes a maximum plasma concentration within minutes, while psychotropic effects start within seconds to a few minutes, reach a maximum after 15 to 30 minutes, and taper off within 2 to 3 hours. Following oral ingestion, psychotropic effects set in with a delay of 30 to 90 minutes, reach their maximum after 2 to 3 hours, and last for about 4 to 12 hours, depending on dose and specific effect.

The initial volume of distribution of THC is small for a lipophilic drug, equivalent to the plasma volume of about 2.5-3 L, reflecting high protein binding of 95-99%. The steady state volume of distribution has been estimated to be about 100 times larger, in the range of about 3.5 L per kg of body weight. The lipophility of THC with high binding to tissue and in particular to fat, the major long-term storage site, causes a change of distribution pattern over time. Only about 1% of THC administered IV is found in the brain at the time of peak psychoactivity. THC crosses the placenta and small amounts penetrate into the breast milk.

Metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation catalyzed by enzymes of the cytochrome P-450 complex. In man, the C-11 carbon is the major site attacked. Hydroxylation results in 11-hydroxy-THC (11-OH-THC) and further oxidation to 11-nor-9-carboxy-THC (THC-COOH), which may be glucuronated to THC-COOH beta-glucuronide. Pharmacologically, 11-OH-THC shows a similar profile as THC while THC-COOH is devoid of psychotropic effects. With oral administration higher amounts of 11-OH-THC are formed than with inhalation, reaching similar plasma levels as its parent drug, and contributing significantly to the overall effects of THC.

Franjo Grotenhermen, MD, is affiliated with nova-Institut, Goldenbergstraβe 2, D-50354 Hürth, Germany (E-mail: franjo.grotenhermen@nova-institut.de).

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Metabolic interaction between THC and the non-psychotropic cannabidiol (CBD) is based on inhibition of the cytochrome P-450-3A enzyme by CBD. Repeated administration of all cannabinoids causes induction of some cytochrome P-450 isoenzymes which may result in interactions with other medical and non-medical drugs that are using the same enzymes for metabolism.

KEYWORDS. Cannabis, cannabinoids, pharmacokinetics, marinol, medical marijuana

INTRODUCTION

Among the reasons for the decline of the medical use of cannabis in the first half of the 20th century were the pharmacokinetic properties of THC in oral preparations (tinctures, fatty extracts). With oral use cannabis effects commence in a delayed and erratic manner, making it difficult to titrate the required dose. Overdosing and underdosing of medicinal cannabis preparations of unknown THC content were the inevitable consequences often described by physicians of the 19th century (See 1890).

A basic understanding of the pharmacokinetic properties of cannabinoids is necessary to comprehend many issues in context with their medical use, e.g., interactions between cannabinoids and metabolic interactions of cannabinoids with other drugs, differences in onset of action and differences in systemic bioavailability between the oral, sublingual and rectal route of administration and inhalation.

Other questions of general interest, among them the possible effects of prenatal marijuana exposure and exposure to the nursing baby, possible health and legal consequences of passive smoking, forensic questions of drug detection and several other topics are easier to understand with some insight into absorption, tissue distribution and metabolism of THC.

The focus of this review will be on Δ^9-THC (tetrahydrocannabinol). The pharmacokinetics of some other natural and synthetic cannabinoids will also be presented briefly.

Cannabinoids of the ^{9}-THC Type

Sixty-six phytocannabinoids have been detected, mainly belonging to one of 10 subclasses or types (ElSohly 2002), consisting of the

cannabigerol type (CBG), cannabichromene type (CBC), cannabidiol type (CBD), Δ^9-THC type, Δ^8-THC type, cannabicyclol type (CBL), cannabielsoin type (CBE), cannabinol type (CBN), cannabinodiol type (CBDL), or to the cannabitriol type (CBTL). It is unclear whether some types are artifacts, resulting from oxidation of the respective parent compounds: CBN from Δ^9-THC, CBL from CBC, and CBE from CBD, or through migration of the double bond in Δ^9-THC to the more thermodynamically stable position in Δ^8-THC (ElSohly 2002).

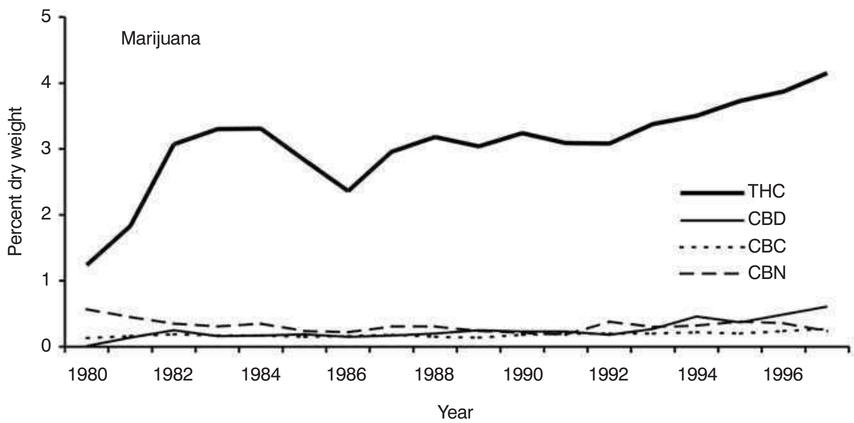
The cannabinoid acids of Δ^9-THC, cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG) are the quantitatively most important cannabinoids present in the plant (see Figures 1 and 2). Cannabinol (CBN), emerging from THC by oxidation, is also often found, particularly in older cannabis samples. Their relative concentrations vary, and plants have been described that mainly contain one of these cannabinoid types.

Nine cannabinoids belong to the Δ^9-THC type with side chains of 1, 3, 4, and 5 carbons (see Table 1). The most abundant compounds are cannabinoids with a C_5 side-chain (Figure 3). Large quantities of propyl homologues (C_3 side-chain) have been found in some samples from the Indian subcontinent (Turner et al. 1980) and from Africa (Pitts et al. 1992), whereas the methyl (C_1 side chain) and butyl homologues (C_4 side chain) are always present in very low concentrations (Vree et al. 1972, Harvey 1976). The cannabinoid composition is determined by genetic and environmental factors. In one study Zambian seedstock plants presented with total tetrahydrocannabivarin (THCV, C_3 side chain) levels greater than tetrahydrocannabinol (C_5 side chain) but the ratio was progressively reversed in succeeding generations of plants grown in the UK (Pitts et al. 1992). In humans, Δ^9-THCV is about one fourth as pharmacologically active as Δ^9-THC (Hollister 1974).

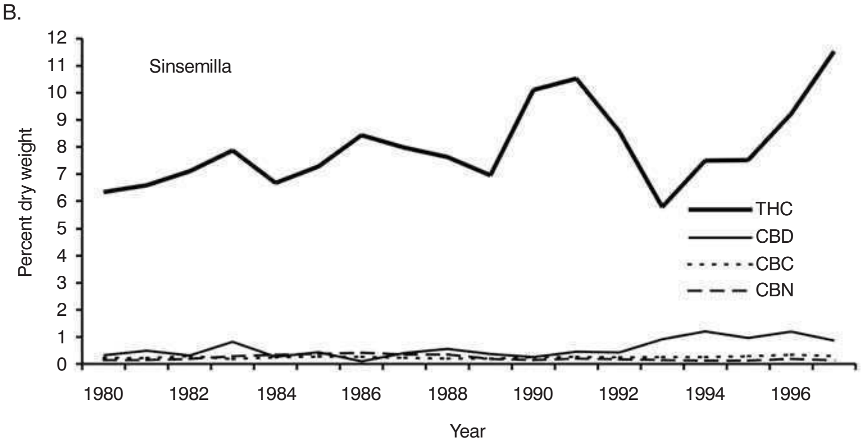
The cannabinoid acids of Δ^9-THC (Δ^9-THCA) are devoid of psychotropic effects (Dewey 1986) and must be decarboxylated to the respective phenols to produce cannabis-like effects. The phenols are also responsible for most of the medicinal effects. More than 90% of the THC in cannabis plants grown in Europe is present as THC acids, while cannabis grown in hot climates of Africa and Asia contain considerable amounts of phenolic THC. The ratio of Δ^9-THC acids to phenolic Δ^9-THC in leaves and flowers of *Cannabis sativa* has been reported to range from 2:1 in Africa (Pitts 1992) to > 20:1 in Switzerland (Brenneisen 1984). In plants grown in the United Kingdom from Moroccan, Sri Lankan and Zambian seedstock, the

FIGURE 1. Average concentrations of the four cannabinoids THC, CBD, CBG, and CBN in confiscated marijuana and sinsemilla between 1980 and 1997 in the USA. Drawn according to data of ElSohly et al. (2000).

A.



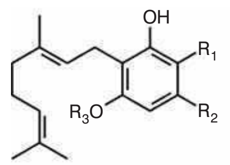
B.



THCA/THC ratio was 17:1 compared with 2:1 in plants from the original areas (Pitts 1992). In several samples of cannabis resin (hashish) the THCA/THC ratio was reported to range between 6.1:1 and 0.5:1, the latter in hashish from India (Baker et al. 1981).

THC decarboxylation in cannabis occurs naturally over time, upon heating (Agurell and Leander 1971, Brenneisen 1984) or under alkaline conditions. Slow decarboxylation of Δ^9-THC occurs at room temperature.

FIGURE 2. Some natural cannabinoids.

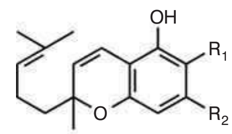


R_1 = H or COOH

R_2 = C_3 or C_5 side chain

R_3 = H or CH_3

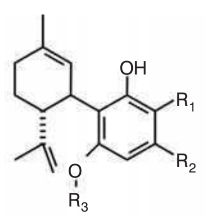
Cannabigerol type



R_1 = H or COOH

R_2 = C_3 or C_5 side chain

Cannabichromene type

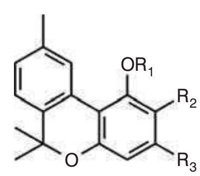


R_1 = H or COOH

R_2 = C_1, $C_{3,}$, C_4 or C_5 side chain

R_3 = H or CH_3

Cannabidiol type



R_1 = H or C_3

R_2 = H or COOH

R_3 = C_1, $C_{3,}$, C_4 or C_5 side chain

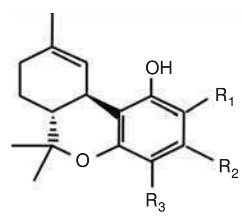
Cannabinol type

Five minutes of heating to 200-210°C have been reported to be optimal for this conversion (Brenneisen 1984), but a few seconds in the blaze of a cannabis cigarette are sufficient as well. Cannabis products with a high content of phenolic THC (e.g., hashish) may be very potent without heating, but usually the potency and medicinal efficacy of cannabis products is significantly increased with smoking the dried plant matter, or by cooking and baking the material.

TABLE 1. Cannabinoids of the Δ^9-*trans*-tetrahydrocannabinol Type (Turner et al. 1980)

Cannabinoid	Abbreviation	R_1	R_2	R_3
Δ^9-*trans*-tetrahydrocannabinolic acid A	Δ^9-THCA	COOH	C_5H_{11}	H
Δ^9-*trans*-tetrahydrocannabinolic acid B	Δ^9-THCA	H	C_5H_{11}	COOH
Δ^9-*trans*-tetrahydrocannabinol	Δ^9-THC	H	C_5H_{11}	H
Δ^9-*trans*-tetrahydrocannabinolic acid-C_4		COOH or H	C_4H_9	H or COOH
Δ^9-*trans*-tetrahydrocannabinol-C_4	Δ^9-THC-C_4	H	C_4H_9	H
Δ^9-*trans*-tetrahydrocannabivarinic acid		COOH	C_3H_7	H
Δ^9-*trans*-tetrahydrocannabivarin	Δ^9-THCV	H	C_3H_7	H
Δ^9-*trans*-tetrahydrocannabiorcolic acid		COOH or H	CH_3	H or COOH
Δ^9-*trans*-tetrahydrocannabiorcol	Δ^9-THC-C_1	H	CH_3	H

FIGURE 3. Cannabinoids of the Δ^9-THC type. The most widespread cannabinoids are the phenolic Δ^9-THC with 21 carbon atoms and a C_5 side chain ($R_2 = C_5H_{11}$) and its two corresponding carboxylic acids A and B (see Table 1).



Natural Δ^9-THC has two chiral centers at C-6a and C-10a in the trans configuration. Usually the acronym THC is applied for this naturally occurring (−)-*trans*-isomer of Δ^9-THC.

Physicochemical Properties and Degradation of ^{9}-THC

(−)-Δ^9-*trans*-tetrahydrocannabinol is defined as (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol with the chemical short formula $C_{21}H_{30}O_2$ and a molecular weight of 314.47 Da. According to the German pharmaceutical monograph, dronabinol contains at least 95% of Δ^9-THC, a maximum of 2% Δ^8-THC and a maximum of 3% other substances, mostly cannabinol and cannabidiol (Kommission Deutscher Arzneimittel-Codex 2001). Dronabinol is avail-

able on prescription for medicinal use in several countries as Marinol™, among them in the USA, Canada, and in some European countries.

At room temperature, Δ^9-THC is a light yellow, resinous sticky oil. Δ^9-THC and many of its metabolites are highly lipophilic and essentially water-insoluble (Garrett and Hunt 1974). Solubility was found to be 2.8 mg/liter in water at 23°(Garrett and Hunt 1974). Calculations of the n-octanol/water partition coefficient (K_{ow}) of Δ^9-THC at neutral pH vary between 6,000 using shake-flask methodology (Mechoulam et al. 1981) and 9,440,000 by reverse-phase high-pressure liquid chromatographic estimation (Thomas et al. 1990). The wide range for aqueous solubility and K_{ow}, may be attributed to the difficulty of uniformly dissolving this essentially water-insoluble substance and accurately measuring small amounts of it. The spectrophotometric pKa is 10.6 (Garrett and Hunt 1974).

Δ^9-THC is thermolabile and photolabile. Storage leads to a decrease in cumulative THC content through oxidation of THC to CBN (Agurell and Leander 1971, Fairbairn et al. 1976). Within 47 weeks, the THC content of dried cannabis leaves and flowers decreased by 7% with dark and dry storage at 5°C, and by 13% at 20°C (Fairbairn et al. 1976). With additional light exposure, the loss increased threefold to 36%. Degradation in hashish occurs much more quickly (Agurell and Leander 1971) since the cannabinoids are no longer protected against oxidation by glandular trichomes. The manufacturer recommends that dronabinol be stored tightly closed, protected from light and in preferably completely filled containers (N. N. Monographs 2001). Stability of THC and two metabolites (11-OH-THC, THC-COOH) in blood and plasma was high for the first month of storage at −10°C, 4°C and room temperature (Johnson et al. 1984). Concentrations of THC stored at room temperature had decreased significantly at 2 months, but was unaltered at 4°C and −10°C for up to 4 months.

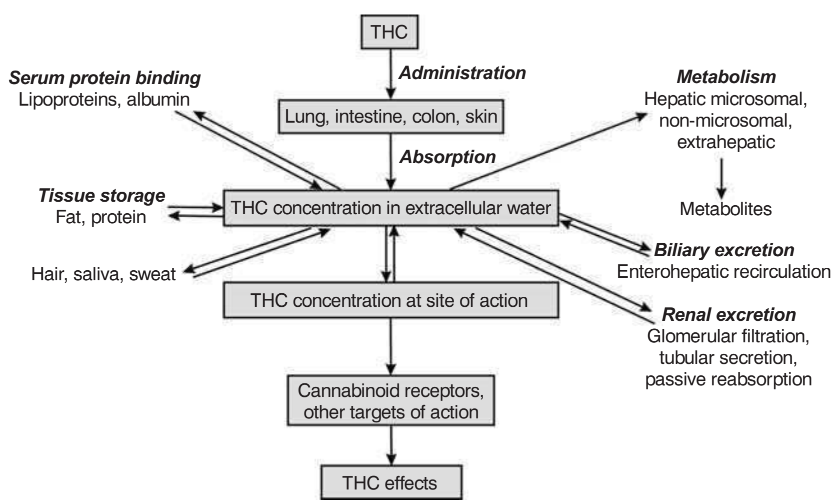
Δ^9-THC rapidly degrades in acid solutions. The kinetics seems to be first order and specific hydrogen-ion catalyzed (Garrett and Hunt 1974), so that significant degradation of THC was assumed to occur in the normal stomach with a $t_{1/2}$ of 1 hr at pH 1.0 (Garrett and Hunt 1974). Thus, a long exposure of THC in the stomach may considerably decrease the potency of oral cannabis preparations, e.g., when taken together with meals that are difficult to digest.

PHARMACOKINETICS OF ^{9}-THC

Most available information on the pharmacokinetics of cannabinoids pertains to Δ^9-THC (Figure 4). Other cannabinoids, among them the phytocannabinoids cannabidiol (Samara et al. 1988) and cannabinol (Johansson et al. 1987) and the synthetic derivative dexanabinol (HU-211) (Brewster et al. 1997), show similar kinetic profiles as the major psychotropic constituent of cannabis. Kinetics of cannabinoids are basically much the same for female and male humans (Wall et al. 1983).

Cannabis products are commonly either inhaled by smoking a cannabis cigarette, taken orally as dronabinol capsules (Marinol™), or in baked foods or liquids (see Figure 4), doses ranging in the order of 2.5-40 mg THC. Various other routes of administration and delivery forms have been tested for therapeutic purposes. The rectal route with suppositories has been applied in some patients (Brenneisen et al. 1996), while dermal (Stinchcomb et al. 2001) and sublingual (Guy and Flint 2000) applications are under investigation. Other methods include eye drops to decrease intraocular pressure (Merritt et al. 1981), as well as aerosols and inhalation with vaporizers to avoid the harm associated with smoking (Williams et al. 1976, Lichtman 2000). In February 2002, Unimed Pharmaceuticals, the marketer of Marinol™ capsules, announced its intention to develop a

FIGURE 4. Pharmacokinetic properties of Δ^9-THC. Modified according to Brenneisen (2002).



metered dose inhaler (MDI) of dronabinol (IACM Bulletin of 3 March 2002).

ABSORPTION

Absorption and metabolism of THC varies according to route of administration. The course of plasma concentration following inhalation is similar to that with intravenous administration with a high peak plasma concentration developing within minutes, which then drops quickly (Wall et al. 1983, Ohlsson et al. 1980a). Oral ingestion results in delayed absorption with a flat plasma course achieving its maximum usually after one to two hours (Ohlsson et al. 1980a, Wall et al. 1983, Frytak et al. 1984) (see Table 2).

Inhalation

Rapid absorption of THC occurs with smoking. THC is detectable in plasma only seconds after the first puff of a cannabis cigarette (Huestis et al. 1992a), with peak plasma concentrations occurring 3 to 10 minutes after onset of smoking (Hollister et al. 1981, Lindgren et al. 1981, Ohlsson

TABLE 2. Systemic Bioavailability of Δ^9-THC Following Inhalation, Oral and Rectal Administration

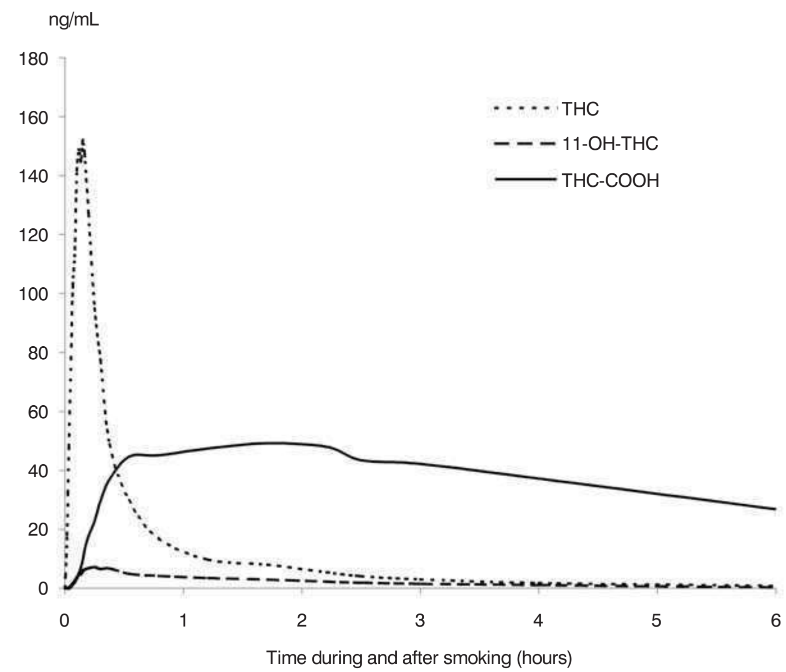
Route	Subjects	Systemic bioavailability (%)		Formulation	References
		Average	Range		
Oral					
	11 frequent or infrequent users	6 ± 3	4-12	THC in chocolate cookie	Ohlsson et al. 1980
	6 men, 6 women	10-20		THC in sesame oil	Wall et al. 1983
	7 men, 10 women	7 ± 3	2-14	THC in sesame oil	Sporkert et al. 1982
Inhalation					
	9 heavy users	23 ± 6	6-56	Marihuana cigarette	Lindgren et al. 1981
	9 light users	10 ± 7	2-22	Marihuana cigarette	Lindgren et al. 1981
	5 heavy users	27 ± 10	16-39	Marijuana cigarette	Ohlsson et al. 1982
	4 light users	14 ± 1	13-14	Marijuana cigarette	Ohlsson et al. 1982
	11 frequent or infrequent users	18 ± 6	8-24	THC in cigarette	Ohlsson et al. 1980
Rectal					
	2 patients with spasticity	190-220% of oral bioavailability		THC-hemisuccinate	Brenneisen et al. 1996

et al. 1980a, Chiang and Barnett 1984, Perez-Reyes et al. 1982b, Huestis et al. 1992a) (see Figure 5).

Systemic bioavailability in several studies ranged between 2 and 56% after smoking a marijuana cigarette, generally between about 10 and 35%, with regular users more efficient (see Table 2). Bioavailability varies according to depth of inhalation, puff and breathholding duration. About 30% of THC in a cannabis cigarette is assumed to be destroyed by pyrolysis. With normal smoking behavior, additional THC is lost in the butt, by side-stream smoke, and by incomplete absorption in the lungs.

A systemic bioavailability of 23 ± 16% (Lindgren et al. 1981) and 27 ± 10% for heavy users (Ohlsson et al. 1982) versus 10 ± 7% and 14 ± 1% for occasional users of the drug was reported. In a study with a smoking machine, patterns of cannabis smoking were simulated with regard to puff duration and volume (Davis et al. 1984), resulting in a figure of 16 to 19%

FIGURE 5. Mean plasma levels of THC, 11-OH-THC, and THC-COOH of six subjects during and after smoking a cannabis cigarette containing about 34 mg THC (drawn from a table of Huestis et al. 1992a).



of THC retention in the mainstream smoke. If the whole cigarette was smoked in one puff, the percentage of THC in the mainstream increased to 69%. Smoking a pipe that produces little side stream smoke may also result in high effectiveness with 45% of THC transferred via the mainstream smoke in one smoker tested (Agurell et al. 1971).

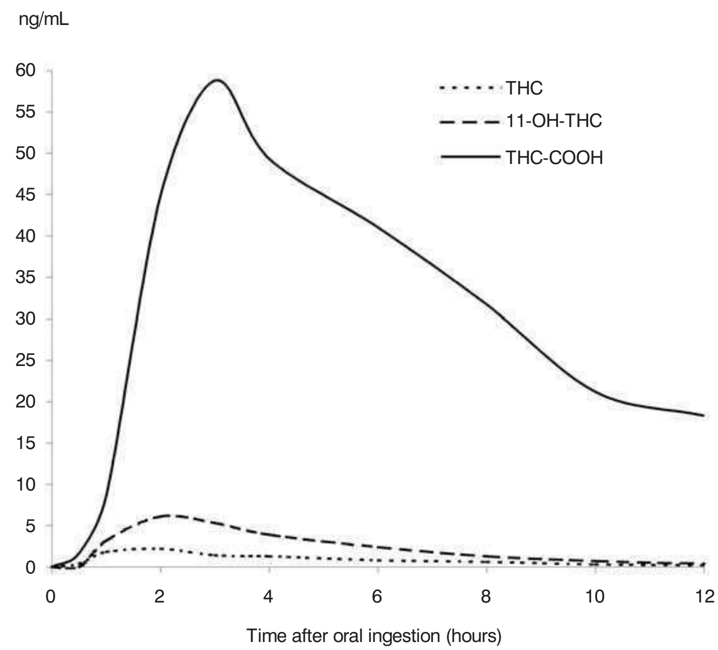
Passive smoking has been shown to result in measurable THC plasma concentrations (Cone and Johnson 1986, Perez-Reyes et al. 1983) and subsequent detection of THC metabolites in the urine (Magerl et al. 1987, Cone et al. 1987, Perez-Reyes et al. 1983). Passive exposure of five drug-free volunteers for one hour to 16 marijuana cigarettes in a small unventilated room on six consecutive days resulted in maximal plasma concentrations of 18.8 ng/ml in one participant and several urine positives with the EMIT cannabinoid assay using a cut-off of 20 ng/ml (Cone and Johnson 1986). However, passive inhalation experiments under conditions likely to reflect realistic exposure consistently resulted in values less than 10 ng/ml of cannabinoids in urine (Mule et al. 1988).

Oral Administration

With oral cannabis use, absorption is slow and erratic, resulting in maximal plasma concentrations usually after 60-120 minutes (Ohlsson et al. 1980a, Wall et al. 1983, Timpone et al. 1997) (see Figure 6). In several studies maximal plasma levels were observed as late as 4 hours (Law et al. 1984), and even 6 hours in some cases (Ohlsson et al. 1980a, Frytak et al. 1984). Several subjects showed more than one plasma peak (Ohlsson et al. 1980a, Hollister et al. 1981). Three daily doses of 15 mg of oral THC did not result in significantly higher THC plasma levels than a single dose (Frytak et al. 1984).

Δ^9-THC is expected to be degraded by the acid of the stomach and in the gut (Garrett and Hunt 1974). At low pH, isomerization to Δ^8-THC and protonation of the oxygen in the pyran ring may occur with cleavage to substituted CBDs (Garrett and Hunt 1974). It has been suggested that a somewhat higher bioavailability is obtained in an oil formulation (Harvey and Brown 1991); however, absorption seems to be nearly complete in different vehicles. Ninety-five percent of total radioactivity of radiolabeled THC was absorbed from the gastrointestinal tract in an oil vehicle (Wall et al. 1983) and 90-95% if taken in a cherry syrup vehicle (Lemberger et al. 1972), but it is unclear from these data how much of this radioactivity was attributable to unchanged THC as opposed to its breakdown products.

FIGURE 6. Mean plasma levels of THC, 11-OH-THC, and THC-COOH of six cancer patients after ingestion of one oral dose of 15 mg THC (estimated from single graphs for each patient of Frytak et al. 1984, with permission). The plasma courses of THC showed considerable interindividual variation (see Figure 8 for the courses of THC plasma concentrations of three patients).



An extensive first pass liver metabolism further reduces oral bioavailability of THC, i.e., much of the THC is initially metabolized in the liver before it reaches the sites of action. Ingestion of 20 mg THC in a chocolate cookie (Ohlsson et al. 1980a) and administration of 10 mg dronabinol (Sporkert et al. 2001) resulted in a systemic bioavailability of 6 ± 3% (range: 4-12%) or 7 ± 3% (range: 2-14%) with a high inter-individual variation (see Table 2).

Ophthalmic Administration

A study in rabbits with THC in light mineral determined a variable systemic bioavailability of 6-40% with ophthalmic administration (Chiang et al. 1983). Plasma concentrations peaked after one hour, and remained high for several hours.

Rectal Administration

With rectal application, systemic bioavailability strongly differed depending on suppository formulations. Among formulations containing several polar esters of THC in various suppository bases, THC-hemisuccinate in Witepsol H15 showed the highest bioavailability in monkeys and was calculated to be 13.5% (ElSohly et al. 1991). The rectal bioavailability of this formulation in man was calculated to be about as twice as high (190-220%) as oral bioavailability in a small clinical study (Brenneisen et al. 1996).

Sublingual Administration

Clinical studies are under way using a liquid cannabis extract applied under the tongue. A phase 1 study in six healthy volunteers receiving up to 20 mg THC was reported to result in "relatively fast" effects (Guy et al. 2000). In phase 2 studies, THC plasma concentrations of up to 14 ng/ml were noted (Notcutt et al. 2001).

Dermal Administration

A few experimental studies have investigated the skin permeation behavior of THC (Touitou and Fabin 1988a, Touitou et al. 1988b, Stinchcomb et al. 2001). In a study using the more stable Δ^8-THC isomer the permeability coefficient of THC was significantly enhanced by water and by oleic acid in propylene glycol and ethanol (Touitou et al. 1988a). Significant THC concentrations in the blood of rats treated with formulations containing 26.5 mg/g THC were measured. Recent studies designed to develop transdermal delivery of cannabinoids found a mean effective permeability coefficient for Δ^9-THC in propylene glycol of 6.3×10^{-6} cm/h (Stinchcomb et al. 2001).

DISTRIBUTION

Tissue distribution of THC and its metabolites are assumed to be governed only by their physicochemical properties, with no specific transport processes or barriers affecting the concentration of the drug in the tissues (Leuschner et al. 1986).

About 90% of THC in the blood is distributed to the plasma, another 10% to red blood cells (Widman et al. 1974); 95-99% of plasma THC is bound to plasma proteins, mainly to lipoproteins (Widman et al. 1974, Hunt and Jones 1980, Wahlqvist et al. 1970, Fehr and Kalant 1974) and less to albumen. Only 5% or less of THC is free for pharmacological activity. The metabolite 11-OH-THC appears to be even more strongly bound than the parent molecule (Harvey 1984). Protein binding of THC metabolites was lower in early phases, with values of 88-93% after 21 and 70 min of intravenous THC application, compared to 92-99% after 240-1,500 min (Hunt and Jones 1980).

The course of plasma concentrations of cannabinoids has been described to correspond to an open two (Wall et al. 1983, Lemberger et al. 1971), three (Barnett et al. 1982, Timpone et al. 1997, Brewster et al. 1995) or four (Hunt and Jones 1980) compartment model. Even five and six compartment concepts have been found in computer models to best fit the THC plasma course in animals (Leuschner et al. 1986). Following an absorption phase, a distribution phase is distinguished from a plasma elimination phase (two compartment model), that may be distinguished from one or more intermediate phases.

The apparent (initial) volume of distribution of THC is small for a lipophilic drug, equivalent to the plasma volume of about 2.5-3 L, reflecting high protein binding that complicates initial disposition. It was reported to be 2.55 ± 1.93 L in drug free users (Hunt and Jones 1980) and 6.38 ± 4.1 in chronic user (Hunt and Jones 1980). The steady state volume of distribution has been estimated to be more than 100 times larger, in the range of about 10 L/kg (Lemberger et al. 1971, Hunt and Jones 1980, Wall et al. 1983). These early data have been questioned because of possible inaccuracy of the quantification methods used. With the use of radiolabeled THC, some metabolites might have been considered to be THC. Based on pharmacokinetic data of two studies (Hollister et al. 1981, Lindgren et al. 1981) that applied gas chromatography/mass spectrometry (GC/MS) for analysis of THC concentration an average volume of distribution of 236 L or 3.4 L/kg (assuming a 70kg body weight) has been calculated (Sticht and Käferstein 1998). Even smaller steady state volumes of distribution of about 1 L/kg have been reported with GC/MS (Kelly and Jones 1992). This volume is still about 20 times the plasma volume since the majority of the lipophilic drug is in the tissues.

Distribution to Tissues and Redistribution

The lipophility of THC with high binding to tissue, and in particular to fat, causes a change of distribution pattern over time (Ryrfeldt et al. 1973). THC distribution may be divided into several phases representing several pharmacokinetic compartments (Leuschner et al. 1986) or different composites of tissues into which the cannabinoid is distributed (Chiang and Rapaka 1987). Hunt and Jones (1980) estimated that 70% of THC initially leaving the central compartment is taken up by tissues and 30% is converted via metabolism. THC rapidly penetrates highly vascularized tissues, among them liver, heart, fat, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid, and pituitary gland, resulting in a rapid decrease in plasma concentration (Ho et al. 1970). Low concentrations were found in the brain, testis and the fetus (Hutchings et al. 1989, Bailey et al. 1987, Ho et al. 1970). Only about 1% of THC administered IV is found in the brain at the time of peak psychoactivity (Gill and Jones 1972). Penetration of the major THC metabolite 11-OH-THC into the brain seems to be faster and higher than that of the parent compound (Perez-Reyes et al. 1976). A ratio of 6:1 has been reported by Gill and Jones (1972). In humans, 11-OH-THC has a similar kinetic profile (Wall et al. 1976) and is as potent as THC in eliciting psychoactive and other effects (e.g., decrease of intraocular pressure) (Perez-Reyes et al. 1972). Thus, it can be expected that the metabolite will significantly contribute to the overall central effects of THC, especially with oral use, but also with inhalation to a lesser degree.

Subsequently intensive accumulation occurs in less vascularized tissues, and finally in body fat (Agurell et al. 1970, Johansson et al. 1989b, Kreuz and Axelrod 1973), the major long-term storage site, resulting in concentration ratios between fat and plasma of up to 10^4:1 (Harvey et al. 1982), while the concentration in the brain was reported to be only three to ten times higher than in plasma (Harvey 1984). Studies with tritium labeled THC determined maximal levels of radioactivity in kidneys and lung after 2 h, whereas after 72 h highest levels were found in spleen and body fat (Agurell et al. 1970), levels in body fat still increasing after 28 days of chronic administration (Kreuz and Axelrod 1973). In humans, up to 193 ng/g of wet tissue were found in fat tissues four weeks after smoking radiolabeled THC (Johansson et al. 1989b). The relatively low concentration in brain is supposed to be due to the fact that the brain is well perfused, moving THC in and out of the brain quickly (Chiang and Rapaka 1987).

The exact composition of the material accumulated in fat is unknown (Harvey 1991), among the possibilities being unaltered THC and its hydroxy metabolites (Kreuz and Axelrod 1973). A substantial proportion of the deposits in fat seems to consist of fatty acid conjugates of 11-OH-THC (11-palmityloxy-THC, 11-stearyloxy-THC, 11-oleyloxy-THC, 11-linoleyloxy-THC) (Haggerty et al. 1986, Leighty et al. 1976). These conjugates have a more lipophilic character than THC itself (Leighty et al. 1976).

Distribution to Fetus and Breast Milk

In animal and man Δ^9-THC rapidly crosses the placenta (Blackard and Tennes 1984). The course of THC levels in fetal blood fairly coincides with that in the maternal blood, though fetal plasma concentrations were found to be lower compared to the maternal level in rats (Hutchings et al. 1989), sheep (Abrams et al. 1985-1986), dogs (Martin et al. 1977), and monkeys (Bailey et al. 1987). The metabolites 11-OH-THC and THC-COOH cross the placenta much less efficiently than THC (Bailey et al. 1987, Martin et al. 1977).

Following oral intake, THC plasma concentrations in the fetus seem to be much lower, about one tenth of the maternal plasma concentration (Hutchings et al. 1989), compared to intravenous and inhalation THC intake, with about one third of the maternal plasma concentration (Martin et al. 1977, Abrams et al. 1985-1986), reflecting differences in metabolism. In humans, THC in cord blood was found to be 3 to 6 times lower than concentrations in maternal blood (Blackard and Tennes, 1984). Thus, oral intake may be less toxic for the fetus compared to inhalation. Additionally, there seems to be a considerable variation in fetal exposure to maternal THC in dependency of placenta function. In a twin study with six dizygotic pairs (where each of the twins has an individual placenta) there were large differences between the pairs in cannabinoid concentrations in hair and meconium (Boskovic et al. 2001). Given that twins are theoretically exposed to similar maternal drug levels, these findings suggest that the placenta may have a major role in modulating the amounts of THC reaching the fetus. The ratio of concentrations in maternal and fetal plasma was maintained with multiple administrations (Martin et al. 1977, Hutchings et al. 1989), indicating that the maternal plasma THC and not the fetal tissue is the actual source for the fetal plasma THC.

THC passes into the breast milk. In monkeys 0.2% of the THC ingested by the mother appeared in the milk (Chao et al. 1976). Chronic adminis-

tration leads to accumulation (Perez-Reyes and Wall 1982a). In a human female the THC concentration in milk was 8.4 times higher than in plasma (Perez-Reyes and Wall 1982a). Thus, the nursing infant might ingest daily THC amounts in the range of about 0.01-0.1 mg from the milk of her mother who is consuming 1-2 cannabis cigarettes a day, assuming an average daily ingestion of 700 ml milk.

Distribution to Saliva and Sweat

THC has been detected in oral fluid (saliva) and forehead wipes (sweat) in 16 of 198 injured drivers admitted to an emergency hospital (Kintz et al. 2000). Concentrations varied between 1 and 103 ng/salivette in oral fluid and between 4 and 152 ng/pad in sweat of the forehead applying GC/MS technology. In a study by Niedbala et al. (2001) with ten volunteers who had been administered single doses of marijuana by smoked and oral routes, THC was detectable in oral fluid for an average of 34 h with a high interindividual variability (range: 1-72), and THC-COOH for 13 h (range: 1-24) by gas chromatography-tandem mass spectrometry (GC-MS-MS) with a 0.5-ng/ml cutoff concentration.

Results of roadside studies using screening devices (immunoassays) for saliva and sweat have provided conflicting results with regard to sensitivity. While screening methods show high sensitivity and specifity for the hydrophilic amphetamines and opiates, they are less sensitive for the lipophilic cannabinoids (Gronholm and Lillsunde 2001). High rates of false negative and false positives have been observed (Samyn and van Haeren 2000, Mura et al. 1999), while others reported good correlation of screening results with later GC/MS analysis of the blood; at least positive results in the screening could mostly be confirmed by GC/MS (Steinmeyer et al. 2001).

METABOLISM

Metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation catalyzed by enzymes of the cytochrome P-450 complex (Matsunaga et al. 1995, Narimatsu et al. 1992), a member of the CYP2C subfamily of isoenzymes playing the major role in humans (Watanabe et al. 1995). Because of its high lipophility, THC needs considerable structural modification to ease excretion. Metabolism of THC occurs fats. In rats more than 80% of intravenous THC was metabolized within 5 minutes (Alozie et al. 1980).

Metabolic rates show relevant interspecies differences that may be in part responsible for some problems of interspecies extrapolation of pharmacological and toxicological effects (Grotenhermen 2002b). Borys and Karler (1979) found three times higher metabolic rates in mice than in rats. Differences in composition of metabolic compounds may be attributed to different profiles of cytochrome P-450 isoenzymes (Harvey and Brown 1991). In humans, allylic oxidation, epoxidation, alphatic oxidation, decarboxylation and conjugation have been described (Chiang and Rapaka 1987) (see Figures 7 and 8).

Besides the liver, other tissues are able to metabolize cannabinoids, but to a much lesser degree, among them the heart and the lung (Nakazawa and Costa 1971, Widman et al. 1975, Harvey and Paton 1976). Nearly 100 metabolites have been identified for THC (Harvey and Brown 1991). Biotransformation of THC produces mono-, di-, and tri-hydroxy metabolites (Wall et al. 1972, Lemberger et al. 1970, Lemberger et al. 1971). Further oxidation results in a series of carboxylic acids and their hydroxy derivatives (Wall et al. 1981).

Major metabolites are monohydroxylated compounds, but the pattern of hydroxylation varies considerably between species (Harvey and Brown 1991). In man (Widman et al. 1978, Halldin et al. 1982, Wall 1971) and many other species, among them mouse, rat, guinea pig, rabbit and gerbil (Harvey and Paton 1976, Harvey and Brown 1991) C-11 is the major site attacked (see Figure 7). Hydroxylation results in 11-hydroxy-THC (11-OH-THC), and further oxidation in 11-nor-9-carboxy-THC (THC-COOH). THC-COOH may be glucuronated to 11-nor-9-carboxy-THC beta-glucuronide. Long-chain fatty acid conjugates of 11-OH-THC are proposed to be a form in which THC may be stored within tissues (Leighty 1973). The C-8 position is also attacked in humans but to a much lesser degree than C-11 (Widman et al. 1978, Halldin et al. 1982a).

Average plasma clearance rates have been reported to be 197 ± 50 ml/min for females and 248 ± 62 ml/min for males (Wall et al. 1983) while others reported higher clearance rates of 760-1190 ml/min (Ohlsson et al. 1982) or 605 ± 149 ml/min for naive THC users and 977 ± 304 ml/min for chronic users (Hunt and Jones 1980) (Table 3). The higher values are similar to the volume of hepatic blood flow, indicating that it is the limiting step of the metabolic rate. These high clearance rates explain the high degree of first pass metabolism, the low systemic bioavailability of THC after oral use and the much higher concentration of 11-OH-THC after oral administration compared to inhalation.

FIGURE 7. Main metabolic pathways of THC.

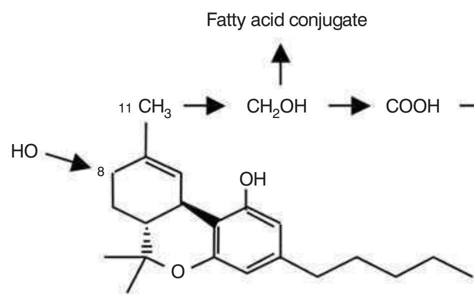
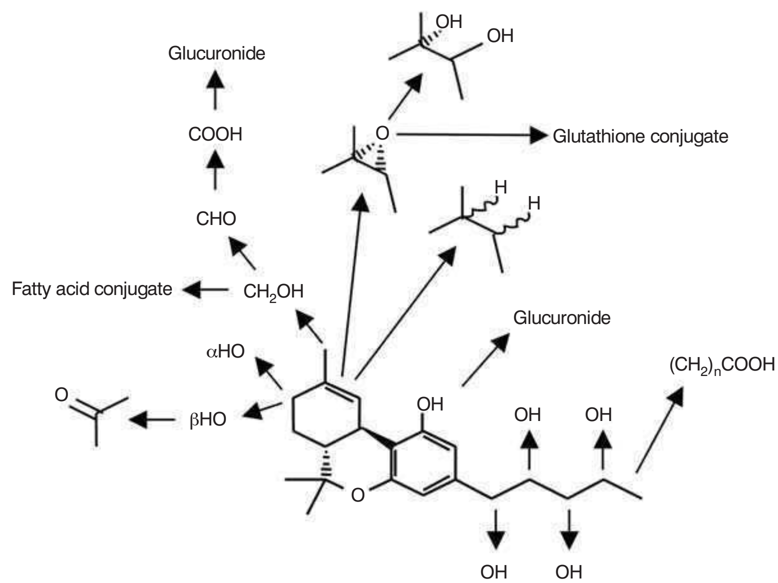


FIGURE 8. Summary of metabolic pathways of THC (modified according to Harvey 1991).



Only slight differences in pharmacokinetic parameters were observed after single and repeat dosing, indicating that the tolerance after chronic THC administration is not or only slightly due to altered metabolism or excretion after repeated dosing (Hunt and Jones 1980). Neither enzyme induction nor enzyme inhibition appear to have much effect on metabolic clearance of THC.

TABLE 3. Pharmacokinetic Data for Δ^9-THC

	Subjects	Dosage (mg)	AUC (ng/ml) × min	C_{max} (ng/ml)	$t_{1/2\beta}$ (h)	V_D (L)	Cl_T (ml/min)	References
Intravenous								
	4 non-users	0.5			57 ± 4	658 ± 174		Lemberger et al. 1971
	5 regular users	0.5			27 ± 1	597 ± 76		Lemberger et al. 1971
	6 males (drug free)	2			19.6 ± 4.1	626 ± 296	605 ± 149	Hunt and Jones 1980
	6 males (chronic)	2			18.7 ± 4.2	742 ± 331	977 ± 304	Hunt and Jones 1980
	6 males	4		70 ± 30	36	734 ± 444	248 ± 62	Wall et al. 1983
	6 females	2.2		85 ± 26	29	523 ± 217	197 ± 50	Wall et al. 1983
	11 males	5	4330 ± 620	161-316				Hollister et al. 1981, Ohlsson et al. 1980
	9 heavy users	5	4300 ± 1670	288 ± 119				Lindgren et al. 1981
	9 light users	5	6040 ± 2.21	302 ± 95				Lindgren et al. 1981
	5 heavy users	5	5180 ± 830		> 20		980 ±150	Ohlsson et al. 1982
	4 light users	5	5460 ± 1180		> 20		950 ± 200	Ohlsson et al. 1982
	4 heavy users	5	9908 ± 3785	438 ± 36	1.9 ± 0.3	75 ± 16	777 ± 690	Kelly and Jones 1992
	4 light users	5	7094 ± 2248	386 ± 29	1.6 ± 0.5	74 ± 35	771 ± 287	Kelly and Jones 1992
Oral								
	6 males	20		14.5 ± 9.7	25			Wall et al. 1983
	6 females	15		9.4 ± 4.5	25			Wall et al. 1983
	11 males	20	1020 ± 320	4.4-11				Hollister et al. 1981, Ohlsson et al. 1980
	3 males	3 × 15		4-6				Frytak et al. 1984
	3 males, 3 females	15		3-5				Frytak et al. 1984
	20 AIDS patients	2 × 2.5		2.01 (0.58-12.48)				Timpone et al. 1997
	7 men, 10 women	10	610 ± 310	4.7 ± 3.0				Sporkert et al. 2001

	Subjects	Dosage (mg)	AUC (ng/ml) × min	C_{max} (ng/ml)	$t_{1/2\beta}$ (h)	V_D (L)	Cl_T (ml/min)	References
Inhalation								
	11 males	19	1960 ± 650	33-118				Hollister et al. 1981, Ohlsson et al. 1980
	9 heavy users	19	2160 ± 1030	98 ± 44				Lindgren et al. 1981
	9 light users	19	1420 ± 740	67 ± 38				Lindgren et al. 1981
	5 heavy users	10	2450 ± 530					Ohlsson et al. 1982
	4 light users	10	1420 ± 340					Ohlsson et al. 1982
	6 males	15.8		84 (50-129)				Huestis et al. 1992a
	6 males	33.8		162 (76-267)				Huestis et al. 1992a

AUC = Area under the curve; C_{max} = Maximum plasma concentration; $t_{1/2\beta}$ = plasma elimination half-life; Cl_T = total clearance; V_D = volume of distribution

COURSE OF PLASMA CONCENTRATION OF THC AND METABOLITES

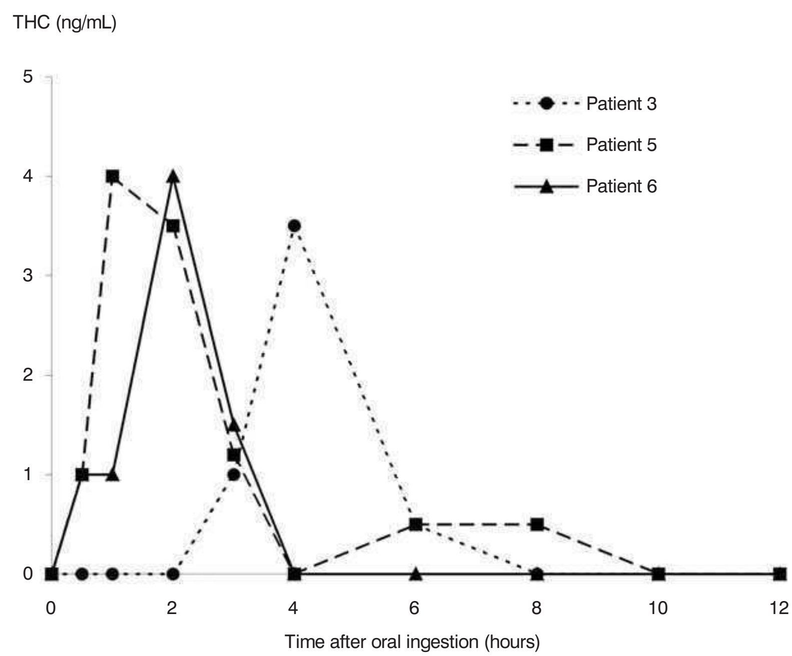
Intravenous infusion of 5 mg THC over 2 min caused average plasma levels within 2 min after the end of infusion of 438 ng/ml in frequent and of 386 ng/ml in infrequent users, that fell rapidly to an average of 25 and 20 ng/ml at 90 min (Kelly and Jones 1992).

The course of plasma THC levels after inhalation resembles that after iv administration (Perez-Reyes et al. 1982b, Huestis et al. 1992a). Smoking a single cannabis cigarette containing 16 or 34 mg THC caused average peak levels of 84.3 ng/ml (range: 50.0-129.0) for the lower dose and 162.2 ng/ml (range: 76.0-267.0) for the higher dose, than rapidly decreased to low levels of about 1-4 ng/ml within 3-4 h (Huestis et al. 1992a) (see Figure 5).

The maximal THC plasma level after smoking a marijuana cigarette (3.55% THC) was reported to exceed the maximal THC-COOH level by threefold and 11-OH-THC by twentyfold (Huestis et al. 1992a). However, THC/11-OH-THC ratios declined and reached a ratio of about 2:1 after 2-3 h (Huestis et al. 1992a). Peak concentrations for THC were observed 8 min (range: 6-10) after onset of smoking. After onset of smoking, 11-OH-THC peaked 15 min (range: 9-23) and THC-COOH peaked 81 min (range: 32-133) (Huestis et al. 1992a).

After oral application the THC plasma concentration shows a flat course with peaks ranging from 4.4-11 ng/ml following 20 mg THC (Ohlsson et al. 1980a), from 2.7-6.3 ng/ml with 15 mg THC (Frytak et al. 1984) and from 0.58-12.48 ng/ml with 2.5 mg THC (Timpone et al. 1997). The plasma course of THC and 11-OH-THC is much more variable than after smoking (see Figure 9). Much higher amounts of 11-OH-THC are formed as with inhalative or intravenous application (Wall et al. 1983, Frytak et al. 1984, Brenneisen 1996). In a study by Wall et al. (1983) the ratio of THC and 11-OH-THC plasma levels in men and women was about 2:1 to 1:1. In several clinical studies (Frytak et al. 1984, Timpone et al. 1997) 11-OH-THC levels even exceeded the THC levels in patients. In a clinical study with 2.5 mg dronabinol daily medium maximal THC levels were 2.01 ng/ml compared to 4.61 ng/ml 11-OH-THC (Timpone et al. 1997).

FIGURE 9. Mean plasma levels of THC, 11-OH-THC, and THC-COOH of three of the six cancer patients of Figure 6 after ingestion of one oral dose of 15 mg THC (estimated from graphs of Figure 2 of Frytak et al. 1984).



ELIMINATION

Elimination from Plasma

About 6 hours after intravenous dosing of THC a pseudoequilibrium is reached between plasma and tissues (Chiang and Rapaka 1987). Concentration in plasma usually has dropped below 2 ng/ml at this time and then decreases more slowly with increasing time from use (Perez-Reyes et al. 1982b, Huestis 1992a). Residual THC plasma levels may persist in frequent cannabis users for several days after last use and may cause difficulties in predicting time of inhalation from THC plasma levels (Huestis et al. 1992b).

After smoking a low dose cannabis cigarette (1.75% THC, about 16 mg) the detection limit of 0.5 ng/ml THC in plasma was reached after 7.2 h (range: 3-12 h) and following a high dose cigarette (3.55% THC, about 34 mg) a plasma concentration of 0.5 ng/ml THC was reached within 12.5 h (range: 6-27 h). Metabolites disappear more slowly. THC-COOH was detectable for 3.5 days (range: 2-7 d) after the low dose and for 6.3 days (range 3-7 days) after smoking the high dose cigarette (Huestis 1992a). After a single oral dose of 20 mg overall Δ^9-THC metabolites reached the detection limit of 0.4 ng/ml in plasma after five days (Law et al. 1984).

The major reason for the slow elimination of THC from the plasma is the slow rediffusion of THC from body fat and other tissues into the blood (Leuschner et al. 1986).

The true elimination half-life of THC from the plasma is difficult to calculate, as the concentration equilibrium ratio plasma/fatty tissue is only slowly reached, resulting in very low plasma levels that are difficult to analyze. In a study by Wall et al. (1983) the terminal phase $t_{1/2\beta}$ ranged from 25-36 h for THC, from 12-36 h for 11-OH-THC and from 25-55 h for THC-COOH after oral or intravenous dosing in man and women. The plasma concentration was followed for 72 h in this study, not long enough to determine the half life accurately. Similar elimination half lives for THC in the range of 20-30 h covering similar periods have been reported by others (Lemberger et al. 1971, Hunt and Jones 1980, Ohlsson et al. 1982).

Longer half-lives of THC plasma elimination have been determined after higher doses and longer periods of measurement in animals (Harvey et al. 1982) and humans (Johansson et al. 1989a). In a study by Johansson et al. (1989a), regular users of cannabis were asked to smoke 56 mg radiolabeled THC during two days and then abstain from all cannabis use.

A terminal half-life of 4.3 ± 1.6 days has been determined in five subjects whose plasma levels were followed for 2 weeks. In two subjects followed for four weeks terminal half-lives of 9.6 and 12.6 d were noted. However, it is unclear whether THC could be reliably distinguished from its metabolites in this study, thus overestimating the length of the half live (Kelly and Jones 1992). Studies using sensitive GC/MC that follow THC plasma concentrations for long periods are needed to determine the elimination half life of THC from plasma. Kelly and Jones (1992) measured a terminal half life for THC of only 117 min for frequent and 93 min for infrequent users, applying GC/MS technology.

The elimination half life for THC metabolites from plasma is longer than the elimination half life of the parent molecule. In a study by Hunt and Jones (1980), the terminal half life of THC for chronic users was 18.7 ± 4.2 h and of the overall metabolites 52.9 ± 3.7 h. In the study by Kelly and Jones (1992), the plasma elimination half life for THC-COOH was 5.2 ± 0.8 days for frequent and 6.2 ± 6.7 days for infrequent cannabis users.

Studies in humans have found no difference in elimination kinetics between heavy and light users (Ohlsson et al. 1982, Hunt and Jones 1980). Differences between regular and casual users in an earlier study (Lemberger et al. 1971) may be attributed to insufficiencies of the detection method (Cone and Huestis 1993). No relevant differences between men and women have been noted (Wall et al. 1981).

Excretion with Urine and Feces

THC is excreted within days and weeks, mainly as metabolites, about 20-35% in urine and 65-80% in feces, less than 5% of an oral dose as unchanged drug in the feces (Wall et al. 1983, Hunt and Jones 1980). After three days overall excretion rates were about 65% following oral, and about 45% with intravenous administration (Wall et al. 1983) (see Table 4). Excretion rates for urine were similar with both routes of application, but excretion rate in feces were substantially higher after oral use.

After smoking cannabis, the urine started to test positive for THC-COOH by GC/MS after an average time of 4 hours (range: 2-8 h) (Niedbala et al. 2001). A single dose of THC may result in detectable metabolites in urine for up to 12 days (Law et al. 1984), usually for 3-5 days (Schwartz et al. 1985). In one study, the average time to the first negative result in urine screening for THC metabolites (enzyme immunoassay with a cutoff calibration of 20 ng/ml) was 8.5 days (range: 3-18 d) for infrequent users and 19.1 days (range: 3-46 d) for regular users (Ellis et al. 1985).

TABLE 4. Mean Cumulative Cannabinoid Excretion According to Wall et al. (1983)

Subjects	Urine (%)		Faeces (%)		Total (%)	% of Total in Urine
	24 h	72 h	24 h	72 h	72 h	72 h
Women Intravenous	11 ± 2	16 ± 3	9 ± 11	26 ± 19	42	38.1
Men Intravenous	10 ± 5	15 ± 4	14 ± 11	35 ± 11	50	30.0
Women Oral	12.5 ± 3.0	15.9 ± 3.6	9 ± 11	48 ± 6	63.9	24.9
Men Oral	10.3 ± 2.1	13.4 ± 2.0	24 ± 42	53 ± 18	66.4	20.2

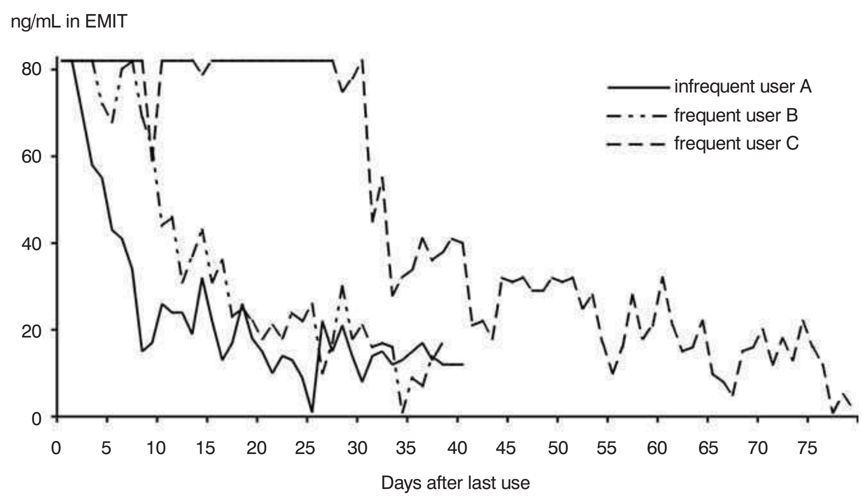
Since urine excretion of metabolites does not monotonously decrease, urine screenings may fluctuate between positive and negative results for several days (see Figure 10). The average time until the latest positive result was 12.9 d (3-29 d) for light users and 31.5 d (4-77 d) for heavy users (Ellis et al. 1985). Similar results with detection times of up to 1-2 months for regular cannabis users and even longer in single cases were reported by others (Daldrup et al. 1988).

An average urinary excretion half life for THC-COOH of about 30 h was observed with a 7-day monitoring period and of 44-60 h with a 14-day period (Huestis et al. 1998). Other groups calculated similar average values of 1.9 and 2 days for frequent and infrequent cannabis users with a 12-day monitoring period (Kelly and Jones 1992) and of about 3 days (range: 0.9-9.8 days) when THC-COOH was measured for 25 days (Johansson and Halldin 1989).

Mainly acids are excreted with the urine of which 18 have been identified (Halldin et al. 1982a, 1982b), the main metabolite being the acid glucuronide of THC-COOH (Williams and Moffat 1980). Free THC-COOH is not excreted in the urine in significant concentration (Law et al. 1984). It was proposed that unconjugated THC-COOH cannot be detected in urine of infrequent users (Alburges and Peat 1986), while others found free THC-COOH concentrations of 1 ± 1.5 ng/ml one day after intravenous administration of THC in casual cannabis smokers (Kelly and Jones 1992). In regular users, free THC-COOH is usually found and was present in concentrations of 2.8 ± 2.7 ng/ml one day after intravenous administration of THC (Kelly und Jones 1992). The detection of 8β,11-dihydroxy-THC above levels of 15-20 ng/ml was proposed to be indicative of use within the previous 4 to 6 hr (McBurney et al. 1986).

Several authors reported that the concentrations of THC and 11-OH-THC in urine were insignificant (Garrett and Hunt 1974, Wall and

FIGURE 10. Course of urine concentration of THC-COOH in one infrequent and two frequent users who abstained from cannabis use at day 0, measured with enzyme immunoassay (EMIT) (drawn according to data of Ellis et al. 1985).

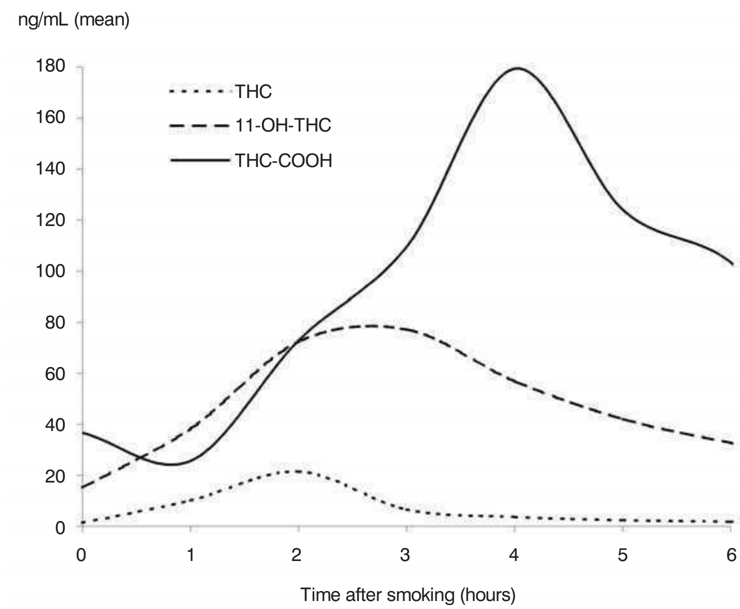


Perez-Reyes 1981), but a recent study found significant concentrations of these neutral cannabinoids using an enzymatic hydrolysis step in the extraction protocol, with THC concentrations peaking at 21.5 ng/ml (range: 3.2-53.3) after 2 h of smoking 27 mg THC in cannabis cigarettes, 11-OH-THC peaking at 77.3 ± 29.7 ng/ml after 3 h and THC-COOH peaking at 179.4 ± 146.9 ng/ml after 4 h (Manno et al. 2001) (see Figure 11).

Renal clearance is not constant, and has been reported to decrease from a maximum of 20 ml/min at approximately 100 min to 1 ml/min after 4 days of THC administration (Hunt and Jones 1980). The high lipophilicity of THC resulting in complete tubular reabsorption explains the lack of significant renal excretion of the unchanged drug (Garrett and Hunt 1974).

The marked enterohepatic recirculation of metabolites and the high protein binding explains the dominance of fecal excretion. The metabolites in the feces are only present in the non-conjugated form (Wall et al. 1983). Acids metabolites, among them THC-COOH, and neutral metabolites, in particular 11-OH-THC, have been found (Mikes et al. 1971, Wall et al. 1983). Differences in metabolite composition have been reported in

FIGURE 11. Mean urine concentrations of unchanged THC and its major metabolites after smoking a cannabis cigarette containing about 27 mg THC by eight subjects with self-reported history of light marijuana use (1-3 cigarettes per week or less). One subject later admitted regular use and presented with high baseline concentrations of 11-OH-THC and THC-COOH (drawn from a table of Manno et al. 2001).



dependency of route of administration for excretion in both urine and feces. More unaltered THC, less of the hydroxy metabolite and more THC-COOH is excreted in feces after oral compared to intravenous dosing (Wall et al. 1983).

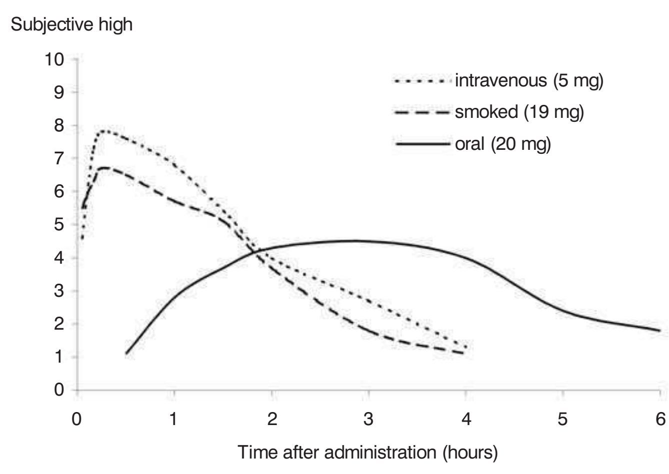
TIME EFFECT RELATIONSHIP

The peak psychotropic effects ("high") after intravenous and inhalative THC application were noted after 20-30 min and decreased to low-level after 3 h and to baseline after 4 h (Hollister et al. 1981, Lindgren et al. 1981, Chiang and Barnett 1984) (see Figure 12). Maximum increase of heart rate was noted within a few minutes (1-5 min), decreasing to baseline after 3 h (Lindgren et al. 1981). Conjunctival injection was noted

within a few minutes and subsided in some participants by 3 h after smoking (Ohlsson et al. 1980a). Duration of maximal effects is dose dependent and was found to be 45 min after 9 mg THC (Harder and Rietbrock 1997) and more than 60 min with higher doses (Robbe 1994).

Following inhalation, THC plasma concentrations have already dropped significantly before maximal psychotropic effects are achieved (Chiang and Barnett 1984, Ohlsson et al. 1980a). A plot of THC plasma levels versus THC effects shows a counterclockwise hysteresis (Chiang and Barnett 1984). During the first 15 minutes the intensity of psychic effects is still rising while plasma levels are falling (Ohlsson et al. 1980a). It has been proposed that the first hour represents the distribution phase (Sticht and Käferstein 1998) and that after 1 h the central compartment has reached equilibrium with effect compartment (Chiang and Barnett 1984). Hence, about 1-4 h after smoking there is a good correlation between plasma level and effects (Chiang and Barnett 1984). There was also a good correlation between THC plasma level and other effects in this phase, with heart rate (Cocchetto et al. 1981) and with psychomotor impairment (Barnett et al. 1985). Overall correlations between log plasma concentrations and ratings of "high" were reported to be moderately positive (r = 0.53) (Ohlsson et al. 1980a), with better correlations at lower THC levels.

FIGURE 12. Time course of subjective effects following three modes of administration. A rating of the degree of "high" was made by subjects on a 0 to 10 scale (estimated from figures of Hollister et al. 1981 and Ohlsson et al. 1980).



After oral use (20 mg THC in a cookie), reddening of the conjunctivae occurred within 30-60 min and was maximal from 60-180 min, gradually lessening thereafter (Ohlsson et al. 1980a). As with inhalation the pulse rate often returned to baseline or below even while the participants felt "high" (Ohlsson et al. 1980a). Psychotropic effects after oral use set in after 30-90 minutes (Wall et al. 1983, Hollister et al. 1981), were maximal between 2 to 4 h, and declined to low levels after 6 h (Hollister et al. 1981). Maximal psychotropic effects usually were delayed for 1-3 h when the plasma levels started to fall (Hollister et al. 1981) (see Figure 13). Correlations between log plasma concentrations and ratings of "high" were reported to be slightly lower compared to inhalation (r = 0.42) (Ohlsson et al. 1980a).

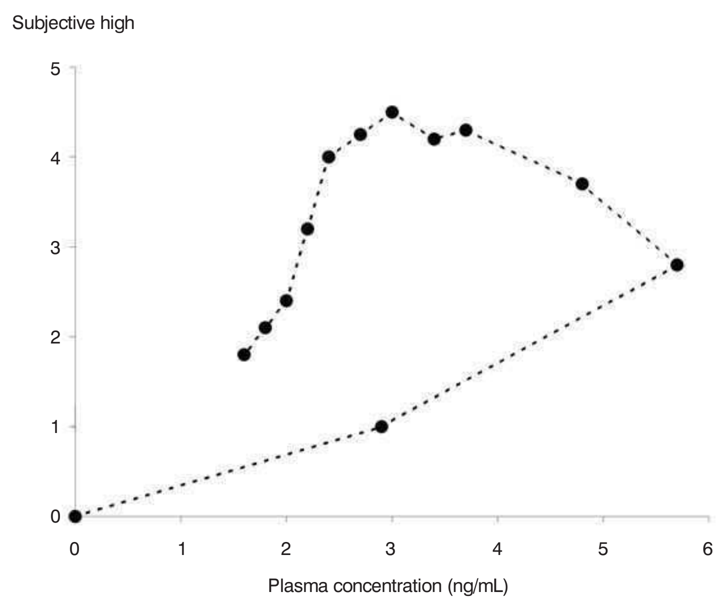
Pharmacokinetic Pharmacodynamic Modeling

With both inhalation and oral use the association between THC levels in the plasma and subsequent psychotropic effects describes a hysteresis over time (see Figure 13). Intensity of THC effects depends on concentration in the effect compartment. THC quickly crosses the blood brain barrier (Nyoni et al. 1996). The short delay in psychotropic THC effects compared to plasma levels is attributed to the time needed to penetrate the barrier and bind the cannabinoid receptors. While plasma levels are already falling, the brain concentrations are still rising (Ohlsson et al. 1980b, Nyoni et al. 1996). In monkeys an IV dose of radiolabelled THC resulted in peak radioactivity levels in the brain after 15-60 minutes in accordance with the time of maximal effect after intravenous and inhalative administration in man (McIsaac et al. 1971). The equilibrium half-life with the effect compartment was calculated to be 29 minutes after smoking a cannabis cigarette (Harder and Rietbrock 1997). Chiang and Barnett (1984) have proposed a kinetic and dynamic model based on an open two compartment model (see Figure 14). Similar kinetic models have been proposed by others (Harder and Rietbrock 1997).

According to the Hill equation there is an association between the intensity of the high effects (E) and the amount of THC in the effect compartment.

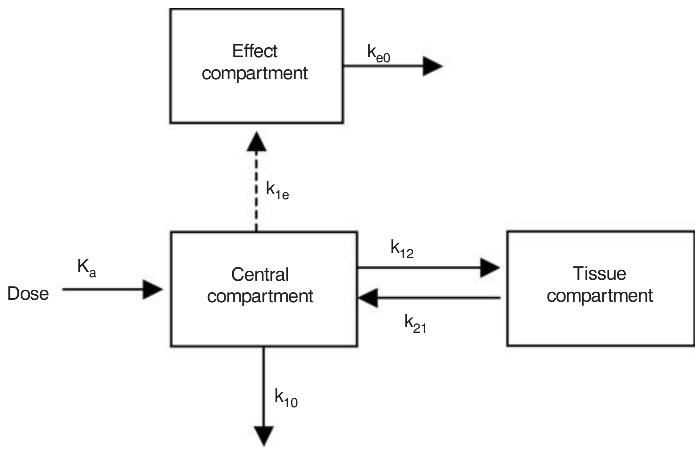
$$E = \frac{\left(k_{e0} * A_e / k_{e1} * V_1\right)^{\gamma}}{\left(k_{e0} * A_e / k_{e1} * V_1\right)^{\gamma} + C_{ss}(50)}$$

FIGURE 13. Phase plots of subjective high/plasma THC levels after oral ingestion of 15 mg THC in a choccolate cookie from 0 to 360 minutes (estimated from figures by Hollister et al. 1981 with some extrapolated data). Every thick point in the figure marks 30 minutes of the whole time. The maximum THC plasma concentration (5.7 ng/ml) was reached after 60 minutes, while the maximum subjective high (on a 0 to 10 scale, see Figure 12) was noted 2-4 hours after intake of the cannabinoid.



The steady-state plasma concentration at the 50% of maximum high effect $C_{ss}(50)$ was ascertained to be 25-29 (ng/ml) by using cannabis cigarettes of three different potencies (Chiang and Barnett 1984). The elimination rate constant from the effect compartment (k_{e0}) ranged from 0.03 to 0.04 min^{-1}, the sigmoid parameter γ (the degree of sigmoidicity of the effect/amount relationship) was 1.5-2.0. The transfer rate constant k_{21} from the tissue compartment was much smaller (0.0078-0.012 min^{-1}) than the elimination rate constant. Thus, the time course of effect must precede the time course of the THC amount in the tissue compartment. The rate constant k_{10} is probably consisting of a mixture of constants for metabolism and distribution between the central and deep tissue compartments (Chiang and Barnett 1984).

FIGURE 14. Kinetic and dynamic model for THC (modified according to Chiang and Barnett 1984). K_a, k_{12}, k_{21}, and k_{10} describe THC kinetics in the empiric two compartment model. The rate constants k_{1e} and k_{e0} characterize the effect compartment.



Predicting Time of Administration

Several models have been applied to predict time of cannabis use from blood concentrations. Recent cannabis use and possible significant impairment was assumed with THC plasma levels of more than 2-3 ng/mL (McBurney et al. 1986) or more than 10 ng/mL (Law and Moffat 1985).

Hanson et al. (1983) were the first to propose the ratio of metabolites to parent molecule for time estimation of last use. Law et al. (1984) stated that a ratio of overall metabolites and THC of < 20 was indicative of recent use, although the ratio could be > 30 in regular users due to accumulation of THC-COOH. Other authors assumed that a THC-COOH/THC ratio < 1 was indicative for use within the past 30 min, a ratio of 2 within one h, a ratio of 3 within two, of 4 within three and a ratio of 7 within 24 h (Garriott et al. 1986).

Huestis et al. (1992b) proposed two mathematical models, derived from linear regression analysis of plasma THC concentration and elapsed time after cannabis use (Model I, r = 0.949), and from linear regression analysis of plasma THC-COOH/THC ratios versus elapsed time after use (Model II, r = 0.919):

Model I: $\text{Log (time in h)} = -0.698 \log [\text{THC}] + 0.687$

Model II: Log (time in h) = (0.576 * [THC-COOH]/[THC]) − 0.176

Medium deviation from the correct time of use was about 1-2 h two to four hours after use and about 2.5-4 h four to eight hours after use (Huestis et al. 1992b). Model I was more accurate following inhalation in infrequent and frequent users, but less reliable with oral use of cannabis, while model II was more accurate for infrequent inhalation and oral ingestion, but tended to overestimate time of usage in frequent users.

Daldrup (1996) proposed a CIF factor (cannabis influence factor) consisting of a ratio of THC together with 11-OH-THC and THC-COOH weighted with constants.

$$CIF = \frac{\dfrac{[THC]}{314.5} + \dfrac{[11\text{-}OH\text{-}THC]}{330.5}}{\dfrac{[THC\text{-}COOH] * 0.01}{344.5}}$$

Individuals with a CIF > 10 were classified as being severely impaired with regard to driving abilities. This author applied Daldrup's equation to data of a paper by Huestis et al. (1992a). A CIF of > 10 was usually reached 2.5-4 h after smoking a marijuana cigarette with great inter-individual variability (Grotenhermen 2001).

PHARMACOKINETICS OF OTHER CANNABINOIDS

The pharmacokinetics of other cannabinoids resembles the kinetics of THC with regard to plasma course, terminal half-lives and other parameters. These will be reviewed briefly for the natural cannabinoids CBD and CBN, for nabilone, a synthetic 9-ketocannabinoid and psychotropic derivative of cannabinol available on prescription in several countries, and for dexanabinol, a non-psychotropic analog of Δ^8-THC under clinical investigation.

Cannabidiol (CBD)

Average systemic bioavailability of inhaled CBD in a group of cannabis users was 31% (range: 11-45%) (Ohlsson et al. 1984). The plasma pattern was similar to that of THC with high levels of about 100 ng/ml within minutes after smoking, and a fast decrease to a concentration of about 10

ng/ml after one hour. After oral administration of 40 mg CBD, the plasma course over 6 h was in the same range as the course after 20 mg THC (Agurell et al. 1981). Daily oral doses of 10 mg/kg CBD per day for 6 weeks in patients with Huntington's disease resulted in mean weekly plasma levels of 5.9-11.2 ng/ml (Consroe et al. 1991). The distribution volume was about 30 L/kg, greater than for THC (Ohlsson et al. 1984). In rats receiving intravenous THC and CBD (1 mg/kg body weight each), brain concentrations of unchanged CBD were higher than that of THC 5 minutes after administration (Alozie et al. 1980).

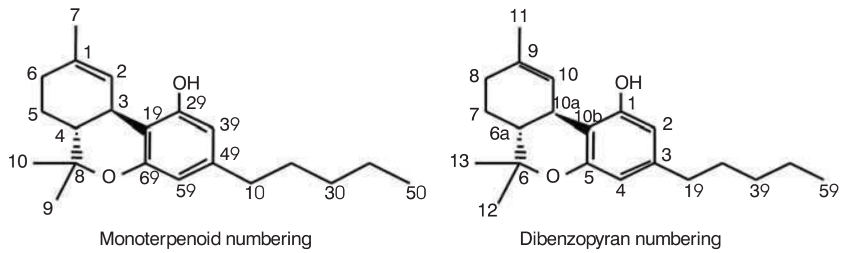
The plasma clearance ranged from 960 to 1560 ml/min (Ohlsson et al. 1984). An average terminal half-life of 24 h (range: 18-33 h) was determined after intravenous injection of 20 mg during an observation period of 72 h (Ohlsson et al. 1984).

Thirty-three metabolites were identified in the urine of a patient treated with CBD and further four metabolites were partially characterized (Harvey and Mechoulam 1990). The metabolic pattern is similar to THC (Wall et al. 1976). The widely used dibenzopyran system for the numbering of cannabinoids cannot be applied to CBD. Metabolites of CBD have to be numbered according to the monoterpene system which can cause some confusion, since the main attacked carbon is numbered C-7 instead of C-11 (see Figure 15), resulting in the hydroxy metabolite 7-OH-THC. Several cyclicized cannabinoids were identified as well, among them Δ^9-THC, Δ^8-THC and cannabinol (Harvey and Mechoulam 1990). The excretion rate of metabolites in humans in urine (16% in 72 h) is similar to that of THC (Wall et al. 1976). Unlike THC, unchanged CBD is excreted in large percentages in the feces (Wall et al. 1976).

Cannabinol (CBN)

Average systemic bioavailability after smoking 19 mg CBN was 26% (range: 8-65%), similar or somewhat higher than the values for THC (Johansson et al. 1987). The plasma course following oral ingestion (Agurell et al. 1981), inhalation (Ohlsson et al. 1985, Johansson et al. 1987) and intravenous administration (Ohlsson et al. 1985, Johansson et al. 1987) was similar to that of CBD. The volume of distribution was determined to 23 L/kg (Johansson et al. 1987). The apparent terminal half lives for CBN were 17 h and 29 h after intravenous administration and smoking, respectively (Johansson et al. 1987). Metabolic patterns in humans were similar to THC with a main attack at C-11 (Wall et al. 1976). Excre-

FIGURE 15. Numbering of cannabinoids. Chemical structure of THC, according to the monoterpenoid system (Δ^1-THC) and dibenzopyran system (Δ^9-THC).



tion was slower with about 8% eliminated with urine and 35% excreted in feces within 72 h (Wall et al. 1976).

Nabilone

The absorption of oral nabilone (Figure 16) (as a polyvinylpyrrolidone coprecipitate) is nearly complete (Lemberger et al. 1982) with plasma levels peaking at 1-4 h. Nabilone was reported to disappear from plasma relatively fast, with a half life of about 2 h (Rubin et al. 1977, Lemberger et al. 1982), while total radioactivity disappeared slowly with a half life of 30 h (Lemberger et al. 1982). Circulating metabolites in plasma include isomeric carbinols with long half lives formed by reduction of the ketone at C-9 (Rubin et al. 1977, Sullivan et al. 1978, Sullivan et al. 1987). About 91% of nabilone was excreted within 7 days, 23% in urine and 67% in the feces (Lemberger et al. 1982).

Dexanabinol (HU-211)

The pharmacokinetics of the synthetic non-psychotropic cannabinoid dexanabinol (HU-211) (Figure 17) was evaluated with doses of 48 mg, 100 mg, and 200 mg as short iv infusions in healthy volunteers. The plasma course best corresponded to a 3-compartment model with a terminal elimination half-life of approximately 9 h (Brewster et al. 1997). The plasma clearance of the drug (about 1,700 ml/min) and the volume of distribution (about 15 L/kg) were somewhat higher than seen with THC.

METABOLIC INTERACTIONS

Interactions of cannabinoids with other drugs may depend on activity on similar effector systems or metabolic interactions (Pryor et al. 1974). Since cannabinoids are strongly bound to proteins, interactions with other protein bound drugs may also occur. However, the latter effect has never been reported.

Metabolic Interactions Between Cannabinoids

Metabolic interaction between cannabinoids has been observed, but only cannabidiol seems to have a significant effect on THC by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system (Watanabe et al. 1987, Bornheim et al. 1998, Jaeger et al. 1996, Yamamoto et al. 1995). Preincubation of human liver microsomes with cannabidiol selectively decreased the formation of tetrahydrocannabinol metabolites catalyzed by cytochrome P450-3A but had no effect on P450-2C9-catalyzed metabolites (Jaeger 1996).

Treatment of mice with high doses of CBD (120 mg/kg) resulted in changes of metabolism of 12 mg/kg THC and modest elevation of THC blood levels (Bornheim et al. 1995). The plasma area under the curve

FIGURE 16. Nabilone.

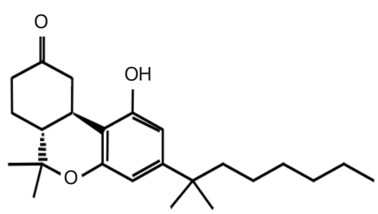
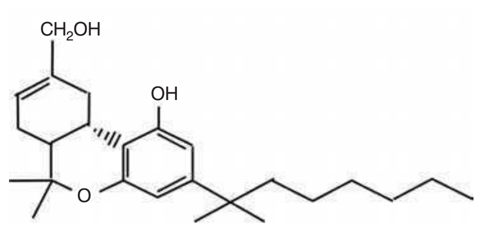


FIGURE 17. Dexanabinol (HU-211).



(AUC) of THC was increased by 50% as a function of decreased clearance, while brain levels of THC increased by nearly 3-fold and brain AUC by 7- to 15-fold (Bornheim et al. 1995). The inhibition of cytochrome P-450 isoenzymes by CBD has been proposed to be a reason for recreational use of cannabis together with other drugs that need cytochrome P-450 for metabolism (cocaine, phencyclidine) (Reid and Bornheim 2001); however, THC and THC metabolites (Bornheim et al. 1994, Watanabe et al. 1986), other cannabinoid receptor agonists (Costa et al. 1996) and even CBD (Bornheim et al. 1994) seem to increase the activity of cytochrome P450 with repeated administration through enzyme induction.

In humans, *pretreatment* with 40 mg oral CBD resulted in a delayed, longer and only slightly reinforced action of 20 mg oral THC (Hollister 1975), while *simultaneous* administration of CBD and THC resulted in a significant block of several THC effects, among them anxiety and other subjective alterations caused by THC (Zuardi et al. 1982), and tachycardia (Karniol 1974), if CBD and THC were given in a ratio of 1:1 or higher, presumably due to antagonistic interaction of CBD at the cannabinoid-1 receptor (Petitet et al. 1998). There were no or only minimal effects of CBD on plasma levels of THC in man (Agurell 1981, Hunt et al. 1981), and there may be a minimal effect on the formation and excretion of metabolites (Hunt et al. 1981).

Metabolic Interactions with Other Drugs

Metabolic interactions of THC with other drugs may occur if these drugs are metabolized by the same isoenzymes of the cytochrome P-450 complex.

A Swiss study found lower plasma levels of the antipsychotic drugs clozapine and olanzapine in smokers of tobacco and cannabis, which was attributed to induction of CYP1A2 of the cytochrome P-450 complex by some smoke constituents (Zullino et al. 2002). Two patients treated with these antipsychotics who stopped smoking experienced adverse drug effects due to increased plasma levels of the drugs, which made dose adjustment necessary (Zullino et al. 2002).

Authors of a case report of a young man who presented with myocardial infarction after taking Viagra® (sildenafil citrate, that is metabolized predominantly by the cytochrome P450 3A4 enzyme) in combination with cannabis supposed that the harmfulness of this combination was mainly due to the inhibition of the cytochrome P450 3A4 isoenzyme by cannabinoids (McLeod et al. 2002). However, it seems more likely that

the combination of the cardiovascular effects of both drugs were the main reason (see Mittleman et al. 2001), since a relevant inhibition of this enzyme by natural cannabinoids would have only been expected with high doses of CBD.

In a clinical study with AIDS patients, there was only a minor influence of cannabis smoking and oral dronabinol on pharmacokinetic parameters of antiretroviral medication used in HIV infection and metabolized by cytochrome P-450 enzymes, and the use of cannabinoids was regarded as unlikely to impact antiretroviral efficacy (Kosel et al. 2002).

Most interactions of cannabinoids with other drugs are not based on metabolic interactions, but on their activity on similar effector systems (Grotenhermen 2002a).

CONCLUSION

With regard to the absorption of cannabinoids efforts are made to compensate the special disadvantages of oral use and inhalation. Sublingual administration of cannabis-based medicines is used in current clinical studies to accelerate the onset of action which is slow and erratic with dronabinol capsules or cannabis confections. The use of vaporizers and the development of inhalers are intended to avoid the harm caused by combustion products inhaled with the smoke of herbal material. Further promising alternatives to the most common routes of administration of today are rectal and transdermal administration, increasing either bioavailability or duration of action.

With regard to distribution and redistribution, cannabinoids cause several problems in forensic science. It is difficult or impossible to assess the actual degree of impairment of drivers from cannabinoid levels in body fluids or to estimate the time of the last consumption. In contrast to the hydrophilic alcohol, cannabinoids are lipophilic and there is only weak correlation between THC levels in the effect compartment (central nervous system) and THC levels in blood or other body fluids. Therefore, it seems reasonable to assess actual impairment with other means, e.g., reactions of the eye pupils to light. Amplitude, contraction speed and dilation speed of the pupils following a defined light stimulus show a dose dependent behavior with maximal effects in the first hour after smoking cannabis and a gradual decline thereafter (Kelly et al. 1993).

Questions of interest with regard to metabolism include different patterns of metabolism in dependency of administration route, and interactions between natural cannabinoids and with other drugs. Since

cannabinoids are metabolized by enzymes of the cytochrome P-450 complex, both decreased (through inhibition by CBD) and increased (through enzyme induction by all cannabinoids) activity of these enzymes may occur. This complex metabolic interaction may be further complicated by other forms of interaction (e.g., interactions at the receptor site). Thus, CBD may reinforce the activity of THC by reducing its metabolic rate and antagonize its activity at the CB_1 receptor site, which may explain contradictory results in studies investigating the interaction of the two phytocannabinoids. In general, it can be expected that metabolic interactions of cannabis products (that usually contain only low amounts of CBD) with other drugs are based more on enzyme induction than on inhibition, but this topic needs further investigation.

The increased formation of 11-OH-THC with oral use compared to inhalation is often made responsible for stronger psychotropic effects of oral cannabinoids. But it seems that this metabolite has a similar pharmacological profile as THC in man and binds to the CB_1 receptor, making it unclear how this metabolic difference may cause differences in effects. There seems to be no relevant difference between single THC and whole plant cannabis taken both orally and inhaled with regard to psychotropic and other subjective effects (Wachtel et al. 2002), supporting the view that the differences in scheduling cannabis and THC (dronabinol) in the narcotics acts of many countries are based more on political than on pharmacological grounds.

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The Acceptance of Medicinal Marijuana in the U.S.

Dale H. Gieringer

ABSTRACT. Medical use of cannabis has become increasingly widespread due to state laws sanctioning its use. The extent of use was estimated by surveying official patient registries, private patients' groups, and physicians specializing in cannabis medicine. As of May, 2002, five states with official registration programs reported a total of over 3,400 patients, ranging from a high of 79 patients per 100,000 population in Oregon to a low of 3 per 100,000 in Colorado. California, which lacks a statewide registration system, has the highest concentration of patients, estimated at 30,000 (89 per 100,000). The rate of usage varies widely between different regions. Some 1% of the population in Mendocino County, California, are legal cannabis patients, while Canadian surveys suggest illegal usage as high as 2%-4%. As many as 5% of registered physicians have recommended marijuana in Oregon. The widespread acceptance of medical cannabis by physicians and patients suggest that marijuana's current Schedule I classification is obsolete.

KEYWORDS. Cannabis, medical marijuana, epidemiology

Cannabis has become increasingly accepted in medical use in the U.S. pursuant to state laws legalizing its use. These are currently operative in

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Dale H. Gieringer, PhD, is Coordinator, California NORML (National Organization for the Reform of Marijuana Laws; Website: www.canorml.org; E-mail: canorml@igc.org).

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eight states: California, Oregon, Washington, Alaska, Nevada, Maine, Colorado and Hawaii. The population of legal medical cannabis patients and their physicians can be estimated from information supplied by state and local patient registration programs and by patients' groups. The following report is based on a telephone survey of such groups conducted by the author in April and May 2002 for California NORML (National Organization for the Reform of Marijuana Laws), one of the original sponsors of California's medical marijuana law, Proposition 215. The results show that medical marijuana is now used legally under state (though not federal) law by tens of thousands of patients and recommended by thousands of licensed physicians. The extent of known usage varies widely among different localities, suggesting considerable potential for further expansion in areas where it is now relatively underutilized.

The question of whether marijuana has "accepted medical use" is relevant to its legal status under federal law. Under the Controlled Substances Act, marijuana is presently classified as a Schedule I drug, which cannot be legally prescribed for medical use. Schedule I is defined to include drugs with "a high potential for abuse" and "no currently accepted medical use in the United States" (21 U.S.C. Section 812(b)(1)). Drugs that do have "accepted medical use" are classified in Schedule II or below and can be legally prescribed. In 1991 the Drug Enforcement Administration rejected a rescheduling petition by the Alliance for Cannabis Therapeutics and NORML, in which it was argued that marijuana did have accepted medical use. The DEA overturned the findings of its own administrative law judge, Francis Young, who, based on hearings from medical experts, had determined that marijuana did in fact have "accepted medical use." In overruling Judge Young, the DEA adopted new regulations re-defining "accepted use" to require "adequate and well-controlled studies of efficacy." The DEA's decision was upheld by the U.S. Court of Appeals on the grounds that the agency had a "reasonable basis" to exercise its regulatory powers in this fashion. Since that time, the medical use of marijuana has greatly expanded following its recognition under state law, beginning in California in November, 1996. A reconsideration of its scheduling status would therefore seem to be in order, though it remains to be seen whether the DEA's regulations will be bent to acknowledge the broader, public acceptance of medical marijuana use in the United States.

The most precise data on medical cannabis usage come from those states that have a mandatory patient registration system, namely Oregon, Alaska, Nevada, Colorado, and Hawaii. In these states, patients who register are protected from criminal laws against possession and cultivation of small amounts of marijuana. In order to register, patients must obtain a

valid recommendation from a licensed physician for a condition covered under the law. Typically, the latter include cancer, AIDS, glaucoma, and diseases involving muscle spasticity or chronic pain.

Although the law presents a strong incentive for patients to register, not all choose to do so. Many are mistrustful of revealing their names to the government out of fear that they will be targeted by local law enforcement or investigated by federal officials. An even greater obstacle to patients' registration can be the difficulty of obtaining a physician's recommendation. Many patients who find marijuana helpful for otherwise intractable complaints report that their physicians are fearful of recommending it, either because of ignorance about medicinal cannabis, or because they fear federal punishment or other sanctions. This is especially true in regions where the use of marijuana is less familiar and accepted.

As shown in Table 1, the rate of registration in medical marijuana programs ranges by over an order of magnitude among different states, from a low of 3.2 per 100,000 in Colorado to 79 in Oregon. Oregon has the most active patients' support network of these states, with a half dozen organizations devoted to helping patients meet registration requirements, teaching them to use and cultivate medical marijuana, or sharing or providing medicine.

The patient population is harder to gauge in states without an official registration system. The most important example is California, the first state to legalize medical marijuana, which has the largest patient population in the nation. California also has the most liberal law, being the only one to allow recommendations for any serious medical condition for which marijuana provides relief. In particular, these include psychiatric problems (e.g. post-traumatic stress disorder, bipolar disorder, attention deficit disorder and substance abuse problems), which are not covered by

TABLE 1. States with Mandatory Patient Registration

	# Patients Registered (May 2002)	# MDs	# Patient Groups	Patients/ 100,000 pop.	Year Program Started
Oregon	2695	> 434	6	79	1999
Alaska	170			27.1	1999
Colorado	138	106	0	3.2	Mar. 2001
Nevada	161	88	0	8.1	Oct. 2001
Hawaii	~300		2	~25	Jan. 2001

other state laws. The California patient population can be roughly estimated from two sources: (1) registration in voluntary patient ID card programs operating in certain localities, and (2) enrollment in various known patients' groups that maintain their own separate membership lists. The problem is considerably complicated by the fact that many patients belong to multiple ID programs or patient groups while many others belong to none at all.

Table 2 summarizes the patient registration programs that were active in California as of May 2002. By far the largest in the state is the Oakland Cannabis Buyers' Cooperative (OCBC) card program. OCBC cards are officially recognized by the city of Oakland as well as by many patients' clubs and dispensaries throughout the state. The OCBC has validated and enrolled some 15,800 patient members since its inception in 1997. Some 6,000 are current members, meaning that they have enrolled or renewed in the past 12 months. The remainder have moved on to other groups, dropped out of the scene to grow by themselves, or ceased using. The OCBC accepts members from around the state, though the great majority are from the greater San Francisco Bay Area.

The next biggest patient identification program is that of the San Francisco Health Department. Unlike the OCBC, San Francisco accepts patients only from San Francisco and four neighboring counties. There are currently some 3,300 registrants in the San Francisco program, 1 in 8 of whom are caregivers, the rest patients. The San Francisco program is rela-

TABLE 2. California Voluntary Patient Registration Programs

	# Patients	# Physicians	Patients per 100,000	Service Area
Oakland CBC	15,800 total/ 6,000 current	1,150	47 (statewide)	Statewide–esp. Bay Area, N. Cal.
S.F. Health Dept.	2,900	75	75	S.F., Sonoma, Marin, San Mateo, Santa Clara counties
Humboldt Co.	232		184	Humboldt only
Sonoma Med. Assoc.	253		55	Sonoma Co. only
Marin Co.	91		37	Marin only
Mendocino Co.	1,030 (patients and caregivers)		1,193	Mendocino only

tively new, dating from 2000, and overlaps with territory served by the OCBC. Many patients are registered in both programs.

There are several other county registration programs that serve only patients who are resident in the county. All are in Northern California counties that are relatively sympathetic to marijuana. (A new registration program was recently enacted in San Diego, but was not yet in operation at the time of this survey.) Mendocino County, a rural county in the heart of California's marijuana-growing "Emerald Triangle" district, has by far the highest known concentration of registered medical marijuana patients, over 1% of the entire population. Humboldt County, a neighboring Emerald Triangle county, ranks a distant second at 0.2%. The Mendocino program enjoys a higher degree of trust from local patients because it is run by a Sheriff who has been openly supportive of marijuana reform. The Humboldt County program, though run by the Health department, is not as popular, as patients remain deeply distrustful of local law enforcement. Marin County has an identification card program, but it has been plagued by mistrust from the patient community and has especially low participation. (The Marin program was substantially revised in June 2002 to accommodate patients' concerns.) Sonoma County has a unique medical peer review program run by the Sonoma Medical Association. Unlike other programs, the Sonoma program does not offer identification cards to protect patients from arrest. Instead, it validates patients' recommendations based on a peer review of their medical records. The Sonoma program appeals specifically to a minority of local patients who have concerns about obtaining a valid physician's recommendation.

Only a portion of California's legal patient population is counted in local registration programs. Many patients have no official identification card but belong to private clubs or patients' groups that have their own separate enrollment procedures and membership lists. Others simply grow for themselves. California NORML identified 55 patient groups that were active in California as of May 1, 2002. They ranged from purely educational self-help groups to patient cultivation collectives to proprietary dispensaries offering medicine for sale to qualified patients. Slightly more than half of the groups actually dispensed medicine to patients.

Southern California has a notable lack of medical marijuana organizations even though it has two-thirds of the state's population. Only a half-dozen patient groups are presently active there. Since the closure of the Los Angeles Cannabis Research Center (LACRC) by a DEA raid in October, 2001, there remain only two small dispensaries in Southern California serving a couple hundred patients. When the LACRC was operating, it had 960 active members and a total enrollment of 1,300, but it had to

routinely reject many applicants due to lack of capacity. Another club in San Diego with some 400 to 700 enrollees was closed by the police in 2000. The political climate in Southern California has been generally adverse to the formation of active patients' groups.

The San Francisco Bay Area has a heavy concentration of medical marijuana groups. There are a dozen dispensaries in San Francisco alone, plus another dozen in neighboring cities such as Berkeley and Oakland. Most rely on San Francisco or OCBC cards and do not maintain separate membership lists of their own. There are also scattered patients' groups and dispensaries serving outlying, rural areas in Northern California. Patients outside the Bay Area commonly complain about the lack of convenient access to medicine.

Table 3 summarizes the major known patients' groups in California. Included are the number of registered patients reported by groups that enroll members themselves. In order to minimize double-counting, Table 3 excludes the membership figures for clubs that rely on identification cards provided by outside agencies such as OCBC or S.F., since their numbers are included in Table 2 above. A large but unknown number of patients are enrolled in more than one group or program, so there remains considerable overlap in the memberships of different groups. Because a few groups declined to disclose their patient population, the information in Table 3 is incomplete, but may nonetheless serve as a rough gauge of the patient population.

Combining Tables 2 and 3, we see that the gross total of patients reported by local identification programs and private patient groups in California is on the order of 25,000 to 35,000 or more. Of course, a great many of these are duplicates, while an unknown number of other patients are not counted in either table. Overall, an estimate of 30,000 appears reasonable, a figure which is consistent with the number of known physician recommendations, as we shall see below. This works out to 89 patients per 100,000 population. This is a bit higher than the rate in Oregon, perhaps reflecting the fact that the Oregon program is more restrictive.

A striking disparity emerges if we consider California as two states. Over 90% of all the patients in Tables 2 and 3 are registered in Northern California. It should be noted that this group does include a few Southern California patients who have traveled north to register. Interviews with physicians and patients' groups suggest that some 20% of patients may be from Southern California. If we estimate that some 25,000 patients reside in Northern California and 5,000 more in the South, we find a rate of 200 patients per 100,000 population in the North versus only 23 per 100,000 in the South. This regional variation is similar to that between different states

TABLE 3. California Patients Groups by Region

	# Groups	#Patients Enrolled
San Francisco Bay Area		
San Francisco	**13**	**> 3,000**
Oakland/E. Bay	**12**	**> 1,800**
Santa Cruz/South	**3**	**> 280**
Sonoma/Marin	**6**	**~ 900**
North State		
Coastal (Humb./Men.)	**7**	**> 1,500**
(not inc. Humboldt MCC closed 2001:		*1,500 enrolled/400 active)*
N. Valley and Sierras	**7**	**> 950**
(not inc. El Dorado clinic closed 2001		*> 6,000 intakes*
not inc. Sacramento center closed 2001		*1,000-1,500 enrolled/ 200 active)*
South State		
Los Angeles	**3**	**~ 400**
(not inc. LA Cannabis Resource Center closed by DEA raid 10/25/01:		*1,682 enrolled/960 active):*
San Diego	**1**	
(not inc. Cal Alt Med Center: closed April 2000		*700 enrolled/300-400 active)*
Other S. Cal.	**3**	

and appears to reflect differences in patient and physician education, organization, and local politics and culture.

Like California, Washington state and Maine lack official registration systems (Table 4). Washington has a couple of patient groups. The leading one reports that it has seen over 2,200 patients and dealt with over 440 physicians since its founding in 1997. However, not all are necessarily current, legally qualified residents. A more detailed estimate by Martin Martinez, an informed expert on medical cannabis in Washington, puts the number of *current* medical marijuana users *known to patients' groups* at 1,900+ (Martinez 2002). He estimates that only 600+ of these are fully compliant with state law, while the remainder are "qualifiable" but lack valid recommendations. This does not include a large number of patients unaffiliated with any group. In this connection, Martinez notes that 2/3 of all medical marijuana arrests and police incidents involve patients unknown to any group. He also says that one particular medical institution

TABLE 4. States Without Mandatory Registration

	Est. # Patients	# MDs	#Patient Groups	Patients/ 100,000 Pop.	Year Program Started
California	30,000		55	89	Nov. 1996
(N. Cal.)	25,000	1,150+	48	200	
(S. Cal.)	5,000	382+	7	23	
Washington	2,300+	250-440	2	39	1999
Maine	---	---	none	---	2000
British Columbia, Canada	1,750-2,000	~700-1,000	3	45-51	

has signed more than 1,000 recommendations, 400 more than the 600+ valid patients attributed to groups. On this basis, it seems reasonable to estimate that there are at least 2,300 patients using medical marijuana in Washington, not all of them in strict accordance with state law. Martinez estimates the total number of qualified recommending physicians (excluding naturopaths, chiropractors, nurses, etc.) at 250+.

In Maine, there are no known patient groups and no good way to estimate the patient or physician population.

Canada presents a similar situation with regards to medical cannabis. Although Canada has a different legal and medical system from the U.S., its cultural and geographical proximity militate for similar patterns of cannabis use. Although there are no provincial laws regarding medical cannabis, the national government has been constrained to recognize its use under a court decision. Like the U.S. West Coast, the western province of British Columbia has been on the forefront of medical marijuana in Canada. Canada's largest patients' group is the Vancouver Compassionate Use Society, which has been in operation for five years and has registered some 1,800 patients, mostly from British Columbia but also other provinces and the U.S. A number of smaller "compassion clubs" are in operation elsewhere in B.C. and Canada.

Pursuant to the court decision, the Canadian government has moved to establish a national medical marijuana program. In May, 1999, the government established a registration program whereby selected patients could be exempted from marijuana laws. The regulations were revised and made more restrictive in July 2001. Health Canada reports that as of April 2002, 657 exemptees had been registered under the old regulations

and another 205 under the new regulations. Participation has been limited by the fact that the current regulations are quite restrictive (e.g., requiring multiple physicians' notes in most cases). In addition, the incentives for registering are less compelling insofar as criminal enforcement of marijuana law is weaker in Canada than the U.S. As a result, patient groups report that the overwhelming majority of their clients remain outside the system.

Canadian surveys indicate a surprisingly high potential demand for medical marijuana. A poll by Toronto's Centre for Addiction and Mental Health found that 2% of Ontario adults reported using marijuana for medicine (Ogborne 2000). A more recent poll by Health Canada found that fully 4% of the population over age 15 used cannabis for medical purposes without government permission (Ottawa Citizen 2002). Extrapolated to the U.S. population, these figures would imply a potential user population of 4 to 8 million.

It is interesting to compare the current rate of medical cannabis usage to that in the historical legal market pre-1937. Though data from this period are generally lacking, there happens to exist a report on U.S. production of medical cannabis in 1918 by W.W. Stockberger of the U.S. Department of Agriculture (Stockberger 1919). Although the U.S. had relied on foreign imports of *Cannabis indica* up to World War I, a domestic industry developed in response to the disruption of supplies caused by the war. By 1918, the annual U.S. production of pharmaceutical cannabis had reached 59,650 pounds. Assuming a low average potency of 1%, this works out to enough to supply 74,000 patients with a daily oral dose of 10 mg (equivalent to two medium-strength oral THC dronabinol capsules)! Of course, it is by no means clear what proportion of patients used cannabis on a daily basis. The early twentieth century was an era of fading interest in cannabis medicine, and its most common patent medicine indications were for coughs and corns. If, as seems likely, cannabis was most commonly used on an occasional basis, the number of actual users could have easily exceeded 100,000. On a per capita basis, this would be 100 in 100,000 Americans, higher than in any state that currently recognizes medical marijuana.

PHYSICIAN ACCEPTANCE

A growing number of physicians are recommending marijuana for their patients under the terms of state laws, despite the fact that many have been deterred by fears of reprisals from federal drug authorities. Because fed-

eral law specifically bars doctors from "prescribing" marijuana, state laws provide that they issue a "recommendation" or "approval" for patients' medical marijuana use. After California's medical marijuana law was passed, the federal government threatened to punish doctors for recommending marijuana, but the U.S. District Court in Northern California issued an injunction protecting doctors' right to do so on First Amendment grounds of freedom of speech (*Conant v. McCaffrey*). Despite this decision (which is currently in appeal), many physicians and professional medical societies remain nervous about recommending marijuana.

Two states, Colorado and Nevada, provided data on the number of different physicians recommending marijuana (Table 1). In both, the number of patients per physician was less than two, implying that few physicians have extensive experience with medical marijuana. Similar results were reported by the British Columbia Compassionate Use Society, which estimates some 700 to 1,000 physicians for its 1,800 patients. It thus appears that most of these patients are obtaining recommendations through their regular personal physicians.

The situation is considerably different in California, where a number of physicians have taken up the practice of specializing in medical cannabis. Eleven leading specialists were interviewed by the author, all but two of them from Northern California. Altogether, they reported a clientele totaling over 31,900 patients. This figure includes duplicates since many patients see more than one physician. Also included are "inactive" patients who have gone more than 12 months without an examination. The number of cannabis specialists has been growing in the last couple of years with expanding awareness of the medical benefits of cannabis in the medical community. However, many patients still complain of a lack of physicians willing to recommend cannabis even for severe, intractable conditions, especially in the southern part of the state.

Aside from specialists, the OCBC reports that over 1,132 California physicians have provided recommendations, mostly from the Bay Area. In Southern California, the Los Angeles Cannabis Resource Center reports 382 different doctors in its files of 1,682 applicants. From this it can be reasonably estimated that there are over 1,500 physicians recommending marijuana in California, or nearly 2% of the state's resident licensed physicians. This works out to a ratio of 20 patients per physician, higher than other states due to the widespread availability of medical cannabis specialists.

In Oregon, 434 different doctors had written recommendations for medical marijuana as of February 19, 2002 (Colburn 2002). More than 40% of the state's patient population was accounted for by a single spe-

cialist, Dr. Philip Leveque, who had written over 1,000 recommendations. Dr. Leveque was subsequently sanctioned with a license suspension for unprofessional conduct (Kramer 2002, Christie 2002). Despite this, Oregon has the highest known rate of physician recommendations for medical cannabis, amounting to 5% of the state's licensed physicians. The rate in Northern California is probably similar, ignoring the southern state. Washington appears to have a comparably high rate of participation, based on the 440 physicians reported by the Green Cross patients' group in Seattle.

REPORTED USES

The popularity of medical marijuana is to a large extent due to the versatility of its use. Major indications cover a panoply of conditions, including: (1) appetite loss and nausea due to cancer chemotherapy, HIV, hepatitis, etc.; (2) muscle spasticity and seizure disorders from multiple sclerosis, spinal trauma, epilepsy, etc.; (3) chronic pain from neuralgia, migraines, arthritis, injuries, and innumerable other disorders; (4) glaucoma; (5) mood disorders, including depression, post-traumatic stress disorder, bipolar disorder, and attention deficit disorder, and (6) as a "harm reduction" substitute for more dangerous drugs, especially opiates and alcohol.

In examinations of 2,480 California patients, Dr. Tod Mikuriya recorded over 250 distinct ICD-9 indications, all of them for chronic conditions resisting conventional pharmacotherapy (Gieringer 2002). The largest category (46%) used cannabis for analgesia, 27% for mood disorders, 9% for spasms and convulsions, 5% for harm reduction/substitution, and 5% for nausea and cachexia. Because Dr. Mikuriya is a psychiatrist, his practice tends to include more mental disorders and fewer acute physical illnesses such as cancer and AIDS.

Other patient surveys show heavy use for chronic pain. A survey of 965 OCBC patients by Jerry Mandel found 36% with chronic pain and spasticity, 29% with HIV, 15% with mood disorders, and 6% with cancer (Gieringer 2002). The Colorado patient registry reports 57% with chronic pain, 35% with muscle spasms, 23% nausea, and 11% HIV/AIDS (Colorado Medical Marijuana Registry Program Update, April 29, 2002). The British Columbia Compassionate Use Society reports HIV, followed by chronic pain, hepatitis, cancer, and harm reduction patients.

Medical marijuana has been used to relieve a wide variety of rare and obscure diseases with no known effective treatment, among them

nail-patella syndrome, eosinophilia-myalgia syndrome, pseudo-pseudo hyperparathyroidism, Henoch-Schoenlein purpura, osteochondrosis, Meniere's disease, Tietze's disease, patellar chondromalacia, etc. (Gieringer 2002).

Marijuana is also widely used for a number of everyday complaints that are not typically classified as "serious," including insomnia, lower back pain, anxiety, pre-menstrual syndrome, and occasional nausea and pains. While a certain number of patients with these conditions are included in state medical marijuana programs, the great majority are not because they do not meet the standard of "serious illness" necessary to qualify under the law.

CONCLUSION

By any reasonable definition, marijuana has "currently accepted medical use in treatment in the United States." Eight states have officially legalized its medical use. A minimum of 35,000 patients are currently using medical marijuana in accordance with state law in the U.S. Over 2,500 different physicians have recommended it for use by their patients. As many as 5% of all registered physicians have recommended marijuana in Oregon and Northern California. Usage rates vary greatly among different regions. The average usage rate in the general population ranges from 80 to 90 per 100,000 in California and Oregon, where there are numerous patient support groups, to fewer than 10 per 100,000 in Colorado and Nevada, where cannabis medical practice is still underdeveloped. As many as 1% of the population in Mendocino County, California, are legal medical marijuana users, while Canadian surveys suggest illegal medical usage as high as 2%-4% in the general population.

The widespread and growing popularity of medical marijuana and its potential for treating a wide range of conditions indicate a growing role in American medicine. These facts refute marijuana's current Schedule I misclassification as a drug lacking "currently accepted medical use."

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An Interview with Markus Storz: June 19, 2002

Ethan Russo

Russo: Please tell us a bit about your educational background.

Storz: I'm a qualified graphic designer.

Russo: How did you become involved in vaporizer research and development?

Storz: 5 years ago I was looking for a good Vaporizer and couldn't find one to satisfy me, so I started to develop and design one myself. The Volcano is manufactured in Tuttlingen, a town in Southern Germany which is regarded internationally as a center of medical technology. The know-how in the area of medical technology which is available here has already been utilized in the development phase of the Volcano (Figure 1).

Russo: Why should the clinical cannabis patient consider vaporization as an alternative?

Storz: Because the inhalation application of cannabis in many cases is preferable to the oral or other application methods. The effects appear much faster with inhalation and allows the user an easier dosage titration (Figure 2).

Vaporization of cannabinoids is extremely promising when compared to smoking, particularly with regard to the medical utilization of hemp.

Ethan Russo is affiliated with Montana Neurobehavioral Specialists, 900 North Orange Street, Missoula, MT 59802 (E-mail: erusso@blackfoot.net).

Markus Storz is affiliated with Vapormed Inhalatoren, Ehrenbergstr. 39, 78532 Tuttlingen, Germany (www.vapormed.de).

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FIGURE 1. Markus Storz explains the workings of the Volcano at CannaTrade 2002, Bern, Switzerland, March 2002, to Mario Price, Senior Pharmacist, James Paget Hospital, Great Yarmouth, UK (Photo by Ethan Russo).

Russo: What are the advantages and disadvantages of vaporization? Does it eliminate toxic by-products of smoking?

Storz: As is commonly known, the hemp herb (or hashish) is burnt during smoking. Temperatures of approximately 500-700°C are reached during this process.

Vaporization of cannabis, on the other hand, involves the herbal material being heated to a minimum of 185°C, this being the temperature at which THC (tetrahydrocannabinol–the main active ingredient in cannabis) evaporates from the herbal material and blends with air (i.e., being transformed into an inhaled form) (Figure 3).

Vaporization also occurs, in principle, during smoking, with hot gases in smoke flowing through the herbal material, causing the vaporization of active ingredients which then blend with the smoke. However, the heat required there is generated through the combustion of the cannabis,

FIGURE 2. Elke demonstrates inhalation from the Volcano vapor bag at CannaTrade 2002, Bern, Switzerland, March 2002 (Photo by Ethan Russo).

a process which involves serious disadvantages. Smoking entails the unavoidable inhalation of toxic combustion by-products along with the desired ingredients, these being carcinogenic and causing irritation of the respiratory tract and emitting noxious odours (Figure 4).

FIGURE 3. Cannabis before and after vaporization in the Volcano, Hash Marihuana Hemp Museum, Amsterdam, Holland, June 2001 (Photo by Ethan Russo).

The disadvantages of vaporization are, that you require a device which costs much more than a pipe or cigarette papers, and that using a vaporizer effectively is not as easy as smoking a joint.

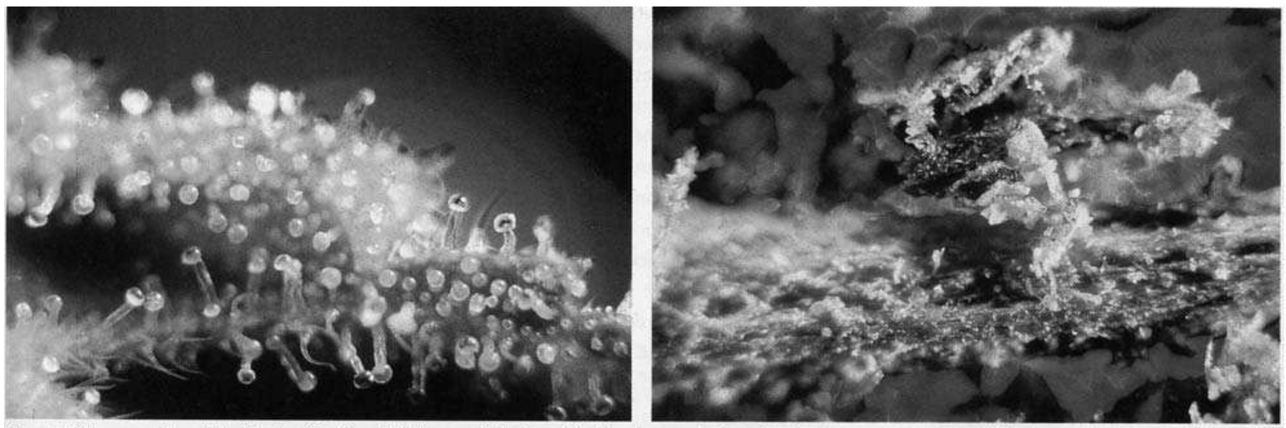
Russo: Could vaporization be done in hospitals or other areas that prohibit smoking?

Storz: Absolutely. No bothersome smoke is created, and non-smokers are not subject to any adverse effects when sharing rooms with users.

Russo: How efficient does the process seem to be? Is there a genuine savings to be achieved as compared to smoking?

Storz: The uncontrolled combustion temperature (which is much too high) causes the unnecessary destruction of the majority of ingredients, thus squandering the original material. Smoking is thus not only damaging to health, but also inefficient.

FIGURE 4. Caption translates as, “Cannabis flowers before and after vaporization.” Note complete disappearance of glandular trichomes from the cannabis.



Cannabisblüten vor und nach dem Verdampfen (Copyright Vapormed, Photograph by Joop Dumay, the Crystalman)

In contrast to this, the use of an effective vaporizer enables one to release with ease 3-4 times the active ingredients in cannabis, while simultaneously reducing the consumption of harmful substances considerably.

Russo: You seem to have taken great care with the materials and construction of your Volcano device. Could you tell us a bit about why you felt that was important?

Storz: This has something to do with my general experience. Whenever I bought a cheap, low quality device, tool, car or whatever, it didn't work as well as the better quality ones and broke after a while. The result always was, I had hassles with the cheap ones, and finally bought the better one, so ended up paying for both. In my opinion, it's just a waste of time and money to buy and use inadequate products.

When I started to design the Volcano, I wasn't thinking about money, I just wanted to create a vaporizer with a design and quality as good as it was possible for me to produce.

Another important point is I feel very responsible for the health of my clients, thus spending a lot of time for research to find harmless materials and assess the general safety of the design.

Russo: How does your device work?

Storz: The most important idea regarding safety and easy use was to separate the process of vaporization from the process of inhalation.

The problem of precise hot air generation is solved by employing an astoundingly simple principle: the air is pumped through a heated aluminium block (similar to an oven with aeration ducts) and thus inevitably assumes the desired temperature. A diaphragm pump ensures that the air flow remains constant, and volumetric flow fluctuations are eliminated. This functions so effectively that electronic controls can be dispensed with. A bimetallic control mechanism is sufficient to ensure a maximum air temperature fluctuation of 8°C (± 4°C) in the filling chamber. This means that the Volcano has the most accurate temperature control of any current available vaporizer. A higher precision is not necessarily essential to vaporize cannabis, but could easily be reached in the Volcano with a much more expensive electronic control.

However, the main distinguishing feature of the Volcano is the patented valve balloon into which the vapor generated is pumped. The valve balloon can be completely detached from the device after filling and the contents inhaled at the user's ease. This ensures that the application is absolutely safe, as

vaporization occurs previously and the user does not come into contact with glass, heat or electricity during inhalation.

Russo: The collecting bag is an interesting feature. Is it chemically inert?

Storz: The balloon is an oven bag as commonly used to bake food for hours in an oven with temperatures up to 200°C. The vapors have a maximum temperature of 130°C when they come out of the Volcano's valve, touching the balloon then the first time. Because of the greater surface area of the balloon, the vapors cool down to ambient temperatures immediately. Oven bags are heatproof, safe for use with food, and absolutely tasteless. They are perfect for use with vapors and can be bought in nearly every supermarket in the world. They don't add anything to the vapor.

Russo: Does not the THC merely coat the bag? How long can the vapor be stored in the bag and still be active?

Storz: Vapors condense as soon as they touch a surface with a lower temperature. But it's not advisable to inhale hot vapors, so the vapors have to be cooled down somehow.

If you want to inhale cool vapor, a partial loss of condensed vapors is unavoidable in every vaporizer design. Once the vapors have cooled down in the balloon to ambient temperatures, it takes hours until the rest coat the bag. I recommend inhaling the vapors, at the latest, 5 or 10 minutes after filling the balloon.

The balloon is not designed to store vapors. It just helps to inhale safely and in comfort, much as a glass helps you to drink easier than drinking directly from the tap of a barrel.

Russo: How many bags can be collected per gram of herbal cannabis?

Storz: This depends on the quality of the cannabis and the size of the balloon, on average approximately 10 balloons.

Russo: How often may a bag be employed? What does it look like when it is fully used?

Storz: Though I recommend changing the balloon earlier, it can be used more than a hundred times.

If you always inhale right after filling the balloon, it looks clean even after a hundred fillings, but then tears may appear making the balloon fill only loosely.

If you "store" the vapors for hours in the balloon, giving them the opportunity to condense completely on the sheath of the balloon, a green-brown layer appears after a few fillings inside the balloon.

Russo: How often does the Volcano unit need be cleaned? What foreign material collects?

Storz: The Volcano (hot air generator) itself is free of maintenance. The mouthpiece, valve and filling chamber should be cleaned regularly to guarantee proper function and a clean taste. As soon as any distinct residue is detected, it is time for cleaning. For hygienic reasons, cleaning of the mouthpiece should also be done before another person inhales. Cleaning the valve parts and changing the balloon should always be done at the same time.

There are no "foreign" materials collected. It's just condensed vapor that can be easily wiped away with pure ethanol and a paper towel.

Russo: Please compare and contrast the Volcano with other vaporizer designs ("frying pan" or bulb)?

Storz: There are essentially two different functional principles by which vaporizers work. One is the "frying pan" principle (i.e., herbal material is distributed on a heated surface and the vapor or smoke which arises from this is inhaled). However, construction restrictions prevent the material being heated in an even manner when employing this method. Such devices are relatively cheap, but ineffective and, consequently, not recommended.

The other method is to permeate the material with a flow of hot air. This achieves a considerably more even heating of cannabis (a prerequisite for controlled vaporization).

The greatest technical difficulty encountered here is heating the air to a pre-specified temperature. THC vaporizes at temperatures of 185°C and over, cellulose (herbal material) beginning to change to cook at 235°C and subsequently combusting.

Theoretically speaking, temperatures between 185°C and 235°C are possible for vaporizing cannabis. However, an effective vaporizer should be capable of achieving air temperature fluctuations of 185°C to a maximum of 205°C in the filling chamber under practical conditions (for reasons relating to flavor, efficiency and avoiding irritating substances). If the fluctuation is lower, it is better.

There are devices with digital displays available that pretend to have an accurate temperature control, but what those displays show is the desired temperature, not the real one in the filling chamber.

One of those vaporizers utilizes a light bulb for heating, meaning that the heating element wires do not contaminate the inhaled air (as they are encapsulated in glass).

Most vaporizers also require that air movement be induced by the users' lungs, resulting in inevitable volumetric flow fluctuations which even well-honed technology cannot compensate for with an adequate degree of precision, particularly if the temperature sensor is not located at the center of activity (i.e., in the filling chamber). The user can, however, attempt to minimize flow fluctuations through a consistent inhalation technique, so that a satisfactory result can eventually be achieved.

Some vaporizers cool and filter vapor with water, a method which results in deposition of a considerable proportion of active ingredients in the water, rather than in the lungs.

There are other "vaporizer"-producers using hot-air-guns (paint-strippers) as a heat source for inhalation purposes.

Russo: I have heard criticism from some cannabis smokers that they do not feel much when they use a vaporizer. Could you please address this contention?

Storz: A Dutch head shop owner told me, his clients, all experienced cannabis users, tell him there are only two kinds of vaporizers giving them a real "hit." These are the Volcano and the ones working with hot air guns, because only with them are you able to inhale a large volume of vapor in one toke. The other ones with the small plastic hoses to inhale from don't produce enough heat to deliver sufficient vapor for a real "kick," but maybe enough for a cannabis patient who requires only small dosages.

Using the Volcano's valve balloon, anyone can inhale in a way that's appropriate for him, because the process of inhalation is separate from the process of vaporization.

Russo: How long should a clinical cannabis patient hold their breath with this device?

Storz: Vaporized natural cannabis irritates the respiratory tract much less than smoked cannabis, but it is not completely free of irritating properties. The cannabis used, the quality of the vaporizer, and the respiratory method employed all have a considerable influence in this respect. It is therefore important that one inhale deliberately, holding ones breath for a

few seconds and then exhaling again. Talking or laughing during inhalation should be avoided, as this can lead to fits of coughing among less experienced consumers. Inhalation of vaporized cannabis for non-smokers becomes easier after a certain individual settling-in period.

Russo: Can the Volcano be employed with hashish, or with "bubble hash?"

Storz: Common hashish and herbal cannabis are perfectly suitable for vaporizers. Cannabis resin in powder form (often erroneously called pollen) can also be used without difficulty. There are a few hashish varieties which become oily or sticky when heated, subsequently smearing the sieve filter. Hash of this kind should be heated previously and mixed with a carrier material (e.g., hemp leaves, sage or peppermint). This prevents blockage of the filters, increases the surface area and also generates interesting flavors. Hashish oil can be used in the same manner.

Another possibility is to dissolve the oil in alcohol, like synthetically-produced pure delta-9 THC (available on prescription in Germany), and trickle it onto the lower screen in the filling chamber, then vaporizing after the alcohol has evaporated.

Russo: Will it work with essential oils?

Storz: The Volcano has an air temperature range from 130°C to 230°C. As far as I know, essential oils should be vaporized at lower temperatures. There are cheaper and better suited devices for this.

Russo: What do you hear from clinical cannabis patients concerning their results with the Volcano?

Storz: They appreciate the easy handling of the Volcano. Some multiple sclerosis patients told me it's impossible for them to roll a joint or use other vaporizers, but it's possible for them to handle the Volcano independently. They just need help when it's time to clean the valve parts of the Volcano or change the balloon.

Russo: Has it been efficient for them?

Storz: If inhaled cannabis helps, the Volcano makes it more efficient and pleasant.

Russo: Have patients reported any changes in their respiratory status after using the Volcano?

Storz: Yes, especially asthma-patients reported they have benefits with vaporized cannabis.

Russo: Are you aware of anyone vaporizing Marinol® with the Volcano?

Storz: No. As far as I know, the THC in Marinol is dissolved in sesame oil. This is not appropriate for vaporization, I think.

Russo: Please address the use of synthetic THC and CBD by vaporization in Germany.

Storz: Compared to natural cannabis, vaporized THC and CBD have the advantage to be free of any irritation during inhalation. The disadvantage of synthetic cannabinoids is the much higher price. In practice, it's easy to vaporize synthetic THC and CBD with the Volcano.

However, the Volcano is not certified as a medical device, yet. Studies of the use of the Volcano with synthetic THC and CBD in various illnesses are just beginning.

Russo: What are the laws in Germany with respect to the use of cannabis with the Volcano?

Storz: Natural cannabis and hashish are illegal in Germany, even for medical use. Synthetic THC, available only on prescription, may be used as pills, and might be used to vaporize, but there are no vaporizers which are certified as medical devices yet.

Russo: To how many countries have Volcano units been shipped?

Storz: We deliver to all countries of the European Community and to Switzerland. That's 17 countries altogether.

Russo: Does that include North America?

Storz: Not yet.

Russo: Will you be planning a unit for the North American market?

Storz: Yes.

Russo: Will you seek Food and Drug Administration (FDA) approval of the Volcano as a medical device?

Storz: Yes, in the medium-term.

Russo: What do you predict for the future of cannabis vaporization and the Volcano?

Storz: As vaporization has lots of convincing advantages compared to smoking, more and more people will quit smoking and start to vaporize cannabis.

Right now the problem is that more than 90% of the available devices on the market don't keep their promise and are simply not suitable for an effective vaporization. I often hear from disappointed users: "Vaporization? Yes, I tried it, but it didn't work well."

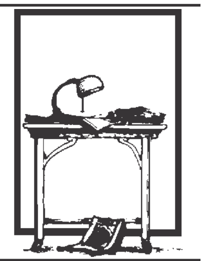
I guarantee, vaporization works fine if you use a good vaporizer.

There are other "vaporizer" producers using hot air guns (paint-strippers) as a heat source for inhalation purposes. When I asked the producers of hot-air-guns what they think about using their paint-strippers for inhalation purposes, they told me not to use it for this, because of the cheap blower-motor (with coal-brushes) emitting carcinogenic coal particles that could be inhaled.

Regarding the future of the Volcano, I have reason to be very optimistic, as this patented invention is a real milestone in development of vaporizers. Anyone who wishes to enjoy the benefits of the vaporization method right now is well advised to try the Volcano.

Russo: Thank you very much for your participation.

EDITORIAL



This issue of *Journal of Cannabis Therapeutics* represents an important turning point, from a previous focus primarily on review articles and surveys.

Heretofore, there has been a dearth of clinical studies of cannabis and cannabinoids due to the daunting task of running the gauntlet of national and international constraints surrounding these modes of therapy. That situation is changing, however slowly.

We begin this issue with three more surveys, which remain of critical importance to physicians and legislators as we assess the attitudes of patients and their results employing cannabis therapeutics. The first is from Ware et al. and concerns attitudes and perceived effects of cannabis in a cohort of Canadian patients with HIV/AIDS. It represents a worthy companion to our previous offerings in *JCANT* 1(3/4), *Cannabis Therapeutics in HIV/AIDS.*

Next, we have a survey of a more general population of THC and cannabis-using patients in Germany by Grotenhermen and Schnelle. Similarities in results and attitudes become apparent across these cultures.

The third survey by Gallagher et al. is from Canada once more, and pertains to attitudes and opinions toward cannabis in a group of palliative care patients. In our aging populations, with an increasing burden of chronic and terminal diseases, such information is of great importance.

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We then transition into initial clinical studies with a review of the presentations from the Cannabinoids in Pain Management Symposium from the American Academy of Pain Management Annual Meeting in Reno, NV. As is apparent, early clinical trial results are arriving on the scene, and will accelerate in the coming months.

Some governments, such as the Netherlands, are allowing physician prescription of cannabis, with supplies available in pharmacies. As a service to our readers, we have included a document on cannabis cultivation guidelines provided by that government, derived from the rules for Good Agricultural Practice of the Working Group on Herbal Medicinal Products of the European Medicines Evaluation Agency (EMEA), first published in the *Dutch State Gazette.* We thank Willem Scholten of the Office of Medicinal Cannabis for providing this translation.

Our next offering will be a special theme double-issue on the state of the art in cannabinoid therapeutics. Its content will consist primarily of Phase II and Phase III double-blind controlled studies of cannabis extracts. We hope that it represents a continuing trend as the pace of research accelerates.

Ethan Russo, MD
Editor

Cannabis Use by Persons Living with HIV/AIDS: Patterns and Prevalence of Use

Mark A. Ware
Sergio Rueda
Joel Singer
Don Kilby

ABSTRACT. This study was undertaken to determine the prevalence of use, reasons for use, amounts and methods used, and perceived effectiveness of cannabis and dronabinol among persons living with HIV/AIDS in Canada.

Cross-sectional anonymous self-administered questionnaire study. Four hundred patients were consecutively recruited from 3 primary care HIV clinics in Toronto, Ottawa and Montreal, and 50 questionnaires were distributed to PHAs (persons having AIDS) at one "cannabis compassion club."

Responses were received from 160 clinic patients and 19 compassion club patients (40% response rate). Of 160 PHAs attending the HIV clin-

Mark A. Ware is affiliated with the Department of Anaesthesia and Family Medicine, McGill University, Montreal, Quebec, Canada.

Sergio Rueda is affiliated with the Community Research Initiative of Toronto, Toronto, Ontario, Canada.

Joel Singer is affiliated with the Canadian HIV Trials Network, University of British Columbia, Vancouver, BC, Canada.

Don Kilby is affiliated with the University of Ottawa, Ottawa, Ontario, Canada.

Address for correspondence to: Dr. Mark A. Ware, McGill Pain Centre, E19.145 Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada H3G 1A4 (E-mail: mark.ware@muhc.mcgill.ca).

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ics, 59 patients (37.3%, 95% CI 29.5-45.1%) reported current use of cannabis. Of 19 compassion club clients, all reported current use of cannabis. Cannabis was most commonly used for stress relief and loss of appetite in both populations, in addition to relief of stress and nausea. Side effects included "high" and dry mouth. Dronabinol and cannabis were also reported to relieve adverse effects of antiretroviral therapy. Dronabinol is less widely used, cannabis being preferred.

Cannabis is commonly used among PHAs for a wide range of symptom relief. Clinical trials using standardized material are required to assess the magnitude of the effects of cannabis, to explore the role of the placebo effect, and to define dose exposures for risk-benefit assessment.

KEYWORDS. Cannabis, marijuana, epidemiology, clinical trials, antiretroviral therapy, knowledge/attitude/practice studies, wasting/nutrition

INTRODUCTION

C*annabis sativa* L. is widely used recreationally and therapeutically in Canada. It is estimated that 28% of the adult Canadian population has ever used cannabis recreationally (World Health Organization 1997). In a recent telephone survey of adults in 2508 Ontario households, 49 people (1.9%) reported using cannabis for a medical reason in the past year, especially pain or nausea, while 173 persons (6.8%) reported recent cannabis use for other reasons (Ogborne et al. 2000). Health Canada has initiated a programme of research to investigate claims of health benefits of cannabis use in a wide variety of diseases (Health Canada 1999). Within this programme, the Community Research Initiative of Toronto (CRIT) and the Canadian HIV Trials Network (CTN) have been asked to conduct a clinical trial of smoked cannabis use among persons living with HIV/AIDS (PHAs).

It has been estimated that between 15-33% of PHAs use cannabis for medical purposes in North America (Braitstein et al. 2001; Dansak 1997; Fairfield et al. 1998; Sidney 2001). Gastrointestinal symptoms (loss of appetite, nausea and vomiting, weight loss) are the most commonly reported reasons for use. However, data on the doses used, the methods of administration, and the frequency and duration of use are not well de-

scribed. In designing a clinical trial, such preliminary data would be useful in establishing a preliminary dosing schedule. Furthermore, PHAs should participate in the identification of clinical endpoints to ensure that the objectives of the trial are relevant to current community practice.

The main psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), has been licensed as dronabinol (Marinol®) for appetite stimulation in PHAs with anorexia (Beal et al. 1997). Little is known of the perception of benefit of dronabinol among PHAs, but anecdotal reports suggest that some PHAs prefer smoked cannabis to dronabinol.

We have conducted a survey to describe the patterns and prevalence of cannabis and dronabinol use among PHAs in Canada.

METHODS

Following community consultations in Toronto and discussions with caregivers across Canada, we designed a 44-item questionnaire on cannabis use among PHAs. The first part of the questionnaire addressed the demographics of the respondent (age, gender), duration of HIV infection, and history of AIDS-defining illness. The second part of the questionnaire addressed patients' experience with dronabinol and cannabis, using identical questions in separate sections for each drug. Only those patients who reported ever having used either cannabis or dronabinol were asked to continue with the questions on those drugs. Questions included reasons for use, ratings of desired and unwanted effects, and reasons for stopping use. At the end of the questionnaire, respondents were asked about their preference for cannabis or dronabinol, and about their interest in participating in clinical trials of cannabis. The questionnaire took less than 15 minutes to complete. Ethics approval was obtained from the CRIT Ethics Review Board and from the Research Ethics Board of the Montreal General Hospital.

Four hundred questionnaires were distributed to patients attending primary care HIV clinics in Toronto, Ottawa and Montreal over a three-week period in mid-2000. A convenience sample of patients was selected by asking a clinic nurse at each site to hand the questionnaire to each consecutive patient entering the clinic during that period, regardless of reason for attendance, with a brief verbal description of the aims of the questionnaire. Patients were informed that their responses would be anonymous, and were asked to return completed forms to the data collection centre using the provided stamped addressed envelopes. A

covering letter accompanying the questionnaire contained a detailed description of the purpose and rationale for the study and a contact number for any questions. No financial incentive was offered. Patients were not asked to provide any information which could be used to identify them. In addition to the HIV clinics, 50 questionnaires were given to one cannabis compassion club for distribution to clients known to be HIV-positive.

Six months after the first questionnaire was handed out, the study was closed. One hundred and sixty responses were received from the HIV clinics at this time, and 19 responses were received from the compassion club, giving an overall response rate of 40%.

Data were entered at the Canadian HIV Trial Network data centre. Missing data were excluded from summary statistics. Categorical responses were summarized with 95% confidence intervals where appropriate. Ratings of drug effects were summarized as frequency distributions. Data analysis was carried out using SAS software.

RESULTS

Patient Demographics

The demographic characteristics of the 160 patients attending the HIV clinics (hereafter called the "clinic" population) and the 19 clients from the compassion club (hereafter called the "club" population) are shown (Table 1). The mean age of the clinic patients was 44.2 years (86.8% male) (range 24-72 years). The mean duration of HIV infection among clinic patients was 8.7 years, with 54 (33.8%) patients reporting having a history of an AIDS-defining illness. Seventy-four (46.3%) patients were cigarette smokers. One hundred forty-five (90.6%) patients reported that they were currently taking antiretroviral therapy.

The mean age of the 19 compassion club clients was 39.5 years (84.2% male) (range 29-51 years). The mean duration of HIV infection among club clients was 8.8 years, and 3 (15.8%) reported having progressed to AIDS. Twelve (63.2%) clients were cigarette smokers, and 16 (84.2%) reported current use of antiretroviral therapy.

HIV Clinic Patients

Prevalence of Cannabis and Dronabinol Use

Of 160 clinic patients, 102 (67.6%; 95% CI 60.1-75.1%) reported ever having used cannabis (Table 2). Fifty-nine patients (37.3%; 95%

TABLE 1. Demographic Characteristics of 160 Clinic and 19 Compassion Club PHAs

Characteristic	Patient population: Clinic (n = 160)	Patient population: Compassion club (n = 19)*
Age (years)		
< 40	60 (37.5%)	10 (52.6%)
40-49	63 (39.4%)	8 (42.1%)
≥ 50	37 (23.1%)	1 (5.3%)
Sex		
Male	139 (86.8%)	16 (84.2%)
Not available	6 (3.9%)	1 (5.3%)
HIV/AIDS status		
Years since HIV positive		
0-4	37 (23.1%)	3 (15.8%)
5-9	58 (36.3%)	8 (42.1%)
≥ 10	65 (40.6%)	8 (42.1%)
Clinical AIDS		
Yes	54 (33.8%)	3 (15.8%)
Not available	9 (5.6%)	-
Current tobacco smoking		
Yes	74 (46.3%)	12 (63.2%)
Not available	2 (1.2%)	-
Current antiretroviral therapy		
Yes	145 (90.6%)	16 (84.2%)
Not available	4 (2.5%)	-

C.I 29.5-45.1%) reported current use of cannabis. Ninety-four patients (92% of ever users) reported ever having used cannabis solely for recreational purposes. Twenty-one patients (14.5%) reported having ever used dronabinol, of whom 10 continued to use dronabinol.

Reasons for Cannabis and Dronabinol Use

Symptom Relief

Of 102 patients who had ever used cannabis, stress relief and loss of appetite were the most common reasons for use (Table 3). The proportion of patients who reported strong or complete relief of their symptoms due to cannabis use is shown (Figure 1). The symptoms reported to be most strongly or completely improved by cannabis were loss of appetite, weight loss, stress, nausea and pain.

TABLE 2. Prevalence of Dronabinol and Cannabis Use Among 179 PHAs

Experience with cannabinoids	Patient population		
	Clinic (n = 160)	(% ± 95% C.I.)	Compassion Club (n = 19)
Cannabis			
Ever used cannabis	102	(67.6 ± 7.5%)	19 (100%)
Recreational cannabis use	94	(63.1 ± 7.7%)	14 (73.7%)
Currently using cannabis	59	(37.3 ± 7.8%)	19 (100%)
Dronabinol			
Ever used dronabinol	21	(14.5 ± 5.7%)	12 (63.2%)
Currently using dronabinol	10	(6.3 ± 4.1%)	2 (10.5%)

TABLE 3. Prevalence of Symptoms for Which Cannabis and Dronabinol Are Used Among PHAs

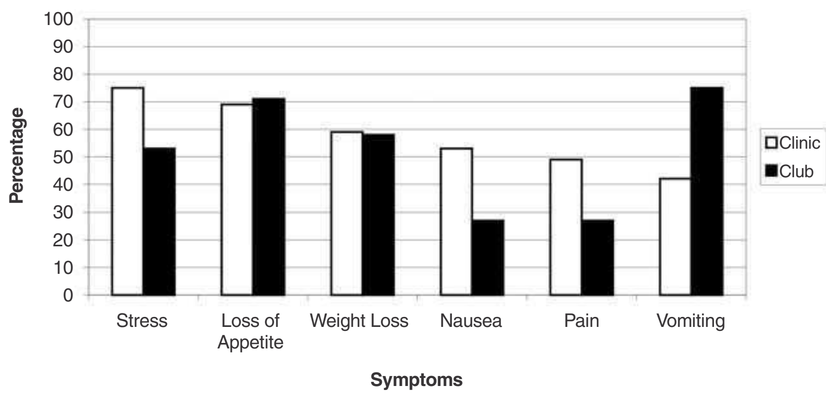
Symptom	Population			
	Clinic		Club	
	Cannabis (n = 102)	Dronabinol (n = 21)	Cannabis (n = 19)	Dronabinol (n = 12)
Stress	58 (57%)	13 (62%)	19 (100%)	7 (58%)
Loss of appetite	51 (50%)	18 (86%)	17 (89%)	11 (92%)
Weight loss	43 (42%)	18 (86%)	11 (58%)	8 (67%)
Nausea	42 (41%)	16 (76%)	14 (74%)	9 (75%)
Pain	36 (35%)	10 (48%)	11 (58%)	6 (50%)
Vomiting	26 (25%)	10 (48%)	8 (42%)	7 (58%)

Of 21 patients who had used dronabinol, loss of appetite, weight loss, and nausea were the most common reasons for use (Table 3). The symptoms reported to be most effectively improved by dronabinol were stress, loss of appetite and weight loss (data not shown).

Experience of Side Effects

Among the 102 clinic patients who had ever used cannabis, overall side effects were felt to be severe in 3 (2.9%), strong in 6 (5.9%), moderate in 18 (17.6%), mild in 36 (35.2%) and absent in 34 (33%) (5 missing). "High" was reported as a side effect in 85 (87%), dry mouth in 64 (63%), drowsiness in 45 (44%), paranoia and palpitations in 27 (26%), and anxiety in 26 (25%) patients. Six patients reported stopping cannabis use because of intolerable side effects.

FIGURE 1. Percentage of PHAs reporting strong or complete relief of symptoms with cannabis use.



Adherence to Therapy

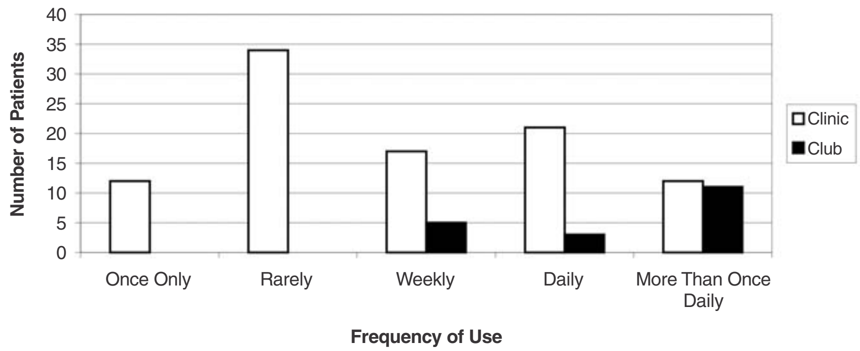
One hundred fourteen (71.3%) clinic patients reported experiencing adverse effects attributable to the use of antiretroviral therapy (ART). Adverse effects contributed to an increase in missed ART doses in 23 (14.4%) of clinic patients. Forty-four (27.5%) patients reported using cannabis or dronabinol to counteract the adverse effects of ART. Data on cannabis and dronabinol separately are not available. Twelve (7.5%) clinic patients reported that use of cannabis or dronabinol reduced the number of ART doses missed.

FREQUENCY OF USE

Of the 102 clinic patients who had ever used cannabis, 96 provided information on the frequency of cannabis use (Figure 2). Of these, 46 (48%) reported cannabis use either once only or rarely.

All 19 of the compassion club clients reported ever having used cannabis, and all 19 continued to use cannabis. Fourteen (73.7%) clients reported having ever used cannabis solely for recreational purposes. Twelve (63.2%) clients reported having ever used dronabinol, with 2 continuing to use dronabinol. Stress (19 clients) and loss of appetite (17 clients) were the most common symptoms for which cannabis was used. Nine clients reported strong or complete relief of loss of appetite (Figure 1). Six clients reported strong or complete relief of vomiting. Fif-

FIGURE 2. Frequency of cannabis use among 96 clinic and 19 compassion club PHAs.



teen (78.9%) clients reported experiencing adverse effects attributable to the use of antiretroviral therapy (ART). These adverse effects contributed to an increase in missed ART doses in 5 (26.3%) clients. Fifteen (78.9%) clients reported using cannabis or dronabinol to counteract the adverse effects of ART, and 6 (31.6%) reported that use of cannabinoids reduced the number of ART doses missed. All club clients reported at least weekly use, with 11 reporting more than once daily use.

Dose Size

For data on cannabis dose size, the information given from the clinic and club responses was combined, and restricted to those reporting current use of cannabis *and* use of cannabis for symptom relief. Data was available from 56 patients. Forty-four (79%) patients reported that a joint was the single dose used, with 32 (57%) patients reporting use once or more per day (Figure 3).

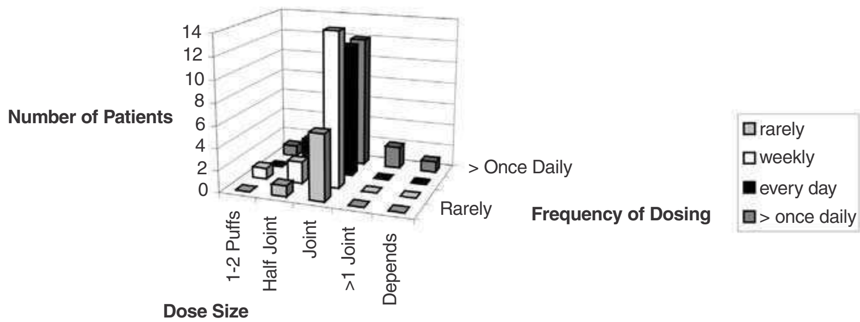
Preference for Cannabis or Dronabinol

Fifty-seven patients reported having used both cannabis and dronabinol (42 clinic, 15 club). Of these, 53 (93%) preferred cannabis (39 clinic, 14 club).

Interest in Clinical Trial Participation

Patients were asked if they would be interested in participating in a clinical trial of cannabis. Of the patients who have ever used cannabis,

FIGURE 3. Dose and frequency of cannabis use among PHAs in Canada (n = 56)



78 (66%) were willing to participate in a trial and 10 (8%) were undecided. Of those who had never used cannabis, 10 (21%) were willing to partake in a trial, and 11 (23%) were undecided. Of the 48 clinic patients using cannabis at least weekly, 43 (90%) stated a willingness to participate in a clinical trial. Of the 46 patients using cannabis rarely, 17 (37%) reported willingness to participate. This preference for trial participation among current frequent users may be related to their experience of side effects of cannabis; of the 46 rare users, 18 (39%) report moderate to severe side effects, while of the 48 weekly users, only 8 (16%) report moderate to severe side effects. Patients who have had unpleasant experiences of adverse effects to cannabis may use cannabis less often, and this may reduce their interest in trial participation.

DISCUSSION

This study attempts to address specific aspects of therapeutic cannabis use among PHAs in Canada, specifically the reasons for use, the perceived effects and the dose and frequency of use. We anticipate that this information will be useful in the design of clinical trials of cannabis for PHAs. Before interpreting the results, we will consider the weaknesses of the study.

The low response rate (40%) among the clinic patients must be considered a potential source of selection bias. Current cannabis users, who may wish to see cannabis more available, may be more likely to respond thus increasing the estimate of prevalence of use. Alternatively, current cannabis users may be less likely to respond given concerns about con-

fidentiality, which would decrease the estimated prevalence. It is difficult to assess the relative contributions of these effects; however, a low response rate is not unusual in studies asking patients about cannabis use (Braitstein et al. 2001; Consroe et al. 1997; Sidney 2001).

Reasons for cannabis use among PHAs were divided into recreational and therapeutic indications. We did not formally distinguish between these two indications in this study, but rather asked patients if they had *ever* used cannabis for symptom control. More precise therapeutic dose estimates may have been possible had we asked more specifically about current cannabis use specifically for symptom management.

The estimates of dose size and frequency must be interpreted carefully, as we did not establish a standard means for estimating amount of cannabis use. We used the term 'joints' to quantify amounts used, but this is bound to mean different things to different people. It does not consider sharing or the size of joints used. Alternative methods, such as calculations of daily requirements from monthly amounts used, require assumptions about frequency of use patterns, which are clearly quite variable. It is clear that dose estimation from survey data is an inexact science, but we may tentatively describe the overall magnitude of dose sizes used in common practice.

Given these limitations, our survey shows that approximately 37% of PHAs attending HIV clinics in Toronto, Montreal and Ottawa are current cannabis users. Although the observed prevalence in this survey was marginally higher than in others reported [33% (Sidney 2001), 32% (Dansak 1997), 23.9% (Fairfield et al. 1998), and 15% (Braitstein et al. 2001)], the margin of error suggests that our results are consistent with previously observed data. We did not follow up the non-responders because of ethical concerns about confidentiality. If we were to assume all non-responders were non-users, the estimate of prevalence of current use would fall to 59/400 (14.8%). It is clear that a significant proportion of PHAs are smoking cannabis, and the risks and benefits of cannabis use on their health need to be examined carefully and objectively.

We found that most current users report relief from loss of appetite, weight loss and nausea. Loss of appetite and nausea have been reported as major reasons for cannabis use in other surveys (Dansak 1997; Fairfield et al. 1998; Harris et al. 2000; Sidney 2001). Our finding of the use of cannabis to relieve stress was also reported in earlier studies (Fairfield et al. 1998; Sidney 2001). We were interested to note the reported use of cannabis to improve side effects associated with ART. The association between pharmaceutical side effects and cannabis use was noted in an earlier retrospective study (Braitstein et al. 2001), and

we have confirmed this here. We suggest that cannabis use may influence ART adherence, and hence affect AIDS-related morbidity and mortality. This hypothesis may be tested in a long-term clinical trial. Clinically meaningful drug-drug interactions between cannabinoids and ART have not been demonstrated among PHAs (Kosel et al. 2002).

With respect to dose strategies, given the limitations mentioned above, we can make some broad observations. PHAs appear to use one or less joints at each dosing point, but frequency of dosing ranges from weekly to more than once daily use. Important questions such as what constitutes a "joint" are not easy to address, but we can gather data from other sources. Compassion club patients in San Francisco report using approximately one ounce (28 g) of herbal cannabis per month (Harris et al. 2000), which would be equivalent to just under a gram a day. Actual amounts of cannabis used may vary between individuals depending on characteristics such as delivery system (joint versus pipe), admixture with tobacco, THC content of cannabis used and smoking characteristics such as length of inhalation and breath holding time. For clinical trials, several methods for reducing this variability are evident. One would be to hold constant the amount of cannabis used and vary the THC content of the cannabis preparation. In addition, the method of smoking may be standardized. Although standardized smoking techniques have been developed (Chait et al. 1988), pharmacokinetic studies have shown that there is still considerable variability in THC absorbed (Huestis et al. 1992). We suggest that the use of a pipe may allow single inhalations of prescribed amounts of cannabis, reducing loss of THC as second hand smoke, which may yield more consistent dose delivery.

We asked patients about interest in participation in clinical trials of cannabis. Of the 50% who were interested, most were current cannabis users. A trial attempting to recruit only cannabis-naïve subjects may therefore give rise to poor enrollment, in addition to ethical concerns of exposing naïve patients to cannabis smoke. We also found that patients interested in participating were more likely to be frequent users reporting less side effects to cannabis than rare users. The selection of only current cannabis users may therefore expose the study to potential biases in terms of expectancy, problems with placebo and blinding, and compliance issues. We suggest that early studies in this population should be restricted to current users on both feasibility and ethical grounds, and the resulting data on safety and dose and effect sizes may help address ethical concerns involving non-users in future studies.

Throughout this study we have tried to obtain information on the comparisons between dronabinol and cannabis. We found that drona-

binol is not as widely used as cannabis, but is used for the same reasons. Patients who had tried both methods preferred smoking cannabis to using dronabinol. The preference for cannabis is widely recognized and has been found in a similar survey (Sidney 2001) in which preference was 98% in favor of cannabis. We did not explore the reasons for this, but suggested reasons have included an improved ability to self-titrate, improved tolerability when faced with nausea and vomiting, and unpleasant side effects of oral THC (Grinspoon and Bakalar 1997).

In summary, we present results of a prospective cross-sectional survey of cannabis use patterns among PHAs in three HIV clinics in Eastern Canada. These data will be useful in designing a clinical trial of smoked cannabis for symptom relief in PHAs. Our results are comparable with those of other PHA populations, and support the justification for clinical trials on the grounds that cannabis is widely used among PHAs, is perceived to be effective at relieving loss of appetite, nausea and stress, and may help patients tolerate antiretroviral therapy.

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Survey on the Medical Use of Cannabis and THC in Germany

Franjo Grotenhermen
Martin Schnelle

ABSTRACT. In recent years, a number of open patient interviews and standardized surveys have been conducted to gain more information concerning subjective experiences with the use of cannabis products in a multitude of medical conditions. After a first effort in 1999 (Schnelle et al. 1999), a second anonymous survey was conducted among patients in the German speech area of Europe concerning use of natural illegal cannabis products and THC, a natural cannabinoid that may be prescribed by German doctors since 1998, and that is also manufactured synthetically.

Questionnaires were distributed to the members of the Association for Cannabis as Medicine (ACM) and additional persons interested in participating. One hundred eighty-two completed questionnaires were sent to the Institute for Oncological and Immunological Research and the ACM, of whom 17 were excluded because these participants apparently did not suffer from severe diseases. Of the 165 respondents included in the final analysis, 61.2% were male and 38.8% were female. Median age was 40.3 ± 12.4 years, with a range of 16 to 87 years.

Twenty-two participants did not use cannabis products for therapeutic purposes. The main reasons were fear of criminal prosecution, the assumption that their doctor will not prescribe THC or a refusal of the doctor to do so.

Among the 143 participants with cannabis or THC experience, the

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Franjo Grotenhermen, MD, is affiliated with the nova-Institut, Goldenbergstraße 2, D-50354 Hürth, Germany (E-mail: franjo.grotenhermen@nova-institut.de).

Martin Schnelle, MD, is affiliated with the Institute for Oncological and Immunological Research, Hardenbergstrasse 19, D-10623 Berlin, Germany (E-mail: martin.schnelle@eifoi.de).

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main diagnosis groups were neurological symptoms (28%) and painful conditions (25.3%), followed by diseases with mainly gastrointestinal symptoms, such as nausea and appetite loss (14%). The most frequent single diagnoses were multiple sclerosis (17.5%), Tourette syndrome (11.9%), HIV/AIDS (10.5%), migraine/headache (4.9%), chronic pain that was not described more precisely (4.2%), hepatitis C (3.5%), depression, sleep disorders, spinal cord injury, and back pain (2.8%, each), asthma, allergy, fibromyalgia, menstrual pain, and epilepsy (2.1%, each).

Average daily THC doses were 14.9 ± 9.5 mg, ranging from 4 to 35 mg. Doses of natural cannabis products (marijuana, hashish) were 1.3 ± 0.9 grams on average (range: 0.02-3.5 g). The drugs were inhaled by 55.9%, employed orally by 16.8%, and 23.1% used both routes of administration.

The cited conditions were much improved by cannabis or THC in 74.8%. An additional 13.3% of patients noted a small improvement, and 2.1% noted no improvement. Others were unsure whether it improved their condition (7.0%), or did not answer this question (2.8%). High satisfaction was reported in 54.5%, 28.0% were satisfied, 14.0% were partly satisfied and 2.1% were not satisfied, while 1.4% did not answer. No side effects were experienced in 73.4%, while 22.4% reported moderate side effects, and 4.2% did not respond. About three-quarters made statements to the consequences of discontinuation of use with regard to withdrawal symptoms. Of these, 67.6% reported no withdrawal symptoms; in 17.6% these symptoms were mild, and in 2.8% they were more severe, while 12.0% reported that they could not evaluate the severity of withdrawal symptoms.

Fifty-three participants noted that they had asked their doctor to prescribe THC. In 54.8% the doctor was willing to do so, but in more than half of the cases (54.9%), the health insurance companies refused to pay for the treatment. There was no association between the reaction of the doctor or of the health insurance and the diagnosis. Most of the participants who reported a refusal by their doctor or the health insurance used illegal cannabis products in the previous month.

Experience with both the medical use of THC and natural cannabis products was reported by 16 participants. There were no clear differences between both drugs with regard to side effects and medicinal efficacy.

In conclusion, this survey adds to an increasing number of patient reports of successful and well-tolerated medical uses of cannabis products in a multitude of conditions. Furthermore, it reflects the division of German doctors and health insurances on the issue.

KEYWORDS. Cannabis, cannabinoids, THC, dronabinol, survey, medical use, dosing, therapeutic effects, side effects, withdrawal, analgesia, neurological disorders, AIDS, multiple sclerosis, spasticity, Tourette syndrome

INTRODUCTION

Cannabis preparations have been used in the treatment of numerous diseases. Reliable data on the efficacy of single cannabinoids or whole plant cannabis in many of these conditions are not available since clinical studies meeting modern standards have only been conducted in a few illnesses for which cannabis products are used, among them side effects of cancer chemotherapy and anorexia associated with cachexia in HIV/AIDS. Additional sources of information of the medical value of cannabis are basic research explaining mechanisms of action, as well as small clinical studies and case reports, e.g., in chronic pain, spinal cord injury, multiple sclerosis, Tourette syndrome, Alzheimer's disease, asthma, and glaucoma.

There is also interest in collecting and utilizing the experience and subjective impressions of patients to provide a more complete picture of the topic. For this reason, surveys have been conducted in the past five years questioning individuals that use cannabis therapeutically. They were conducted either as oral non-standardized interviews in the course of investigations of state or scientific institutions (House of Lords Select Committee on Science and Technology in the UK, Institute of Medicine in the USA), on the therapeutic potential of cannabis (House of Lords 1998, Joy et al. 1999), or as anonymous surveys using standardized questionnaires (Barsch 1996, Consroe et al. 1997, Consroe et al. 1998, TNO 1998, Helliwell 1999, Müller-Vahl et al. 1999, Schnelle et al. 1999, Gieringer 2002).

Clinical studies employing single cannabinoids or, less often with whole plant preparations (smoked marijuana, encapsulated cannabis extract) have often been inspired by positive anecdotal experiences reported by patients employing crude cannabis products, to test whether anecdotal experiences in a certain disease were rare exceptions, or whether a considerable number of patients suffering form this ailment would profit from cannabinoid treatment. Thus, a survey in patients with Tourette syndrome about their use of nicotine, alcohol and cannabis and its effects on clinical symptoms (Müller-Vahl et al. 1997) initiated clinical studies with dronabinol (Δ^9-THC) demonstrating that this

cannabinoid is an effective drug in the treatment of this movement disorder (Müller-Vahl et al. 1999, Müller-Vahl et al. 2002). Clinical studies to investigate anti-emetic, appetite enhancing, anti-spastic and analgesic effects have been inspired by anecdotal reports as well. Several clinical case reports were conducted with the intent to objectify the subjective experience of a patient, and were usually able to do so (e.g., Petro 1980, Meinck et al. 1989, Martyn et al. 1995, Maurer et al. 1990, Schon et al. 1999, Holdcroft et al. 1997, Müller-Vahl et al. 1999).

Anecdotal observations (Chatterjee et al. 2002) and surveys (Ware et al. 2002) remain an important source of knowledge for understanding the medicinal benefits of cannabis preparations and their possible side effects.

Following an initial survey that was conducted between April 1998 and April 1999 (Schnelle et al. 1999), the German Association for Cannabis as Medicine (ACM) in cooperation with the Institute for Oncological and Immunological Research in Berlin conducted a second survey in 2001 to question ACM members and others about their experiences with the medical use of cannabis products, comparisons between natural cannabis and THC, the attitude of their doctors and the reaction of their health insurances when asked to pay for a treatment with THC. At the time of the first survey, there was almost no experience with THC in Germany, as it has only been prescribed since February 1998.

METHODS

In July 2001 the ACM distributed a patient questionnaire to about 700 members in Germany and Switzerland, of whom more than 650 are Germans. An unknown percentage of ACM members are persons who use cannabis products for medical reasons. ACM members and others interested in participating in the survey were asked to complete the questionnaire and return it anonymously to the Institute for Oncological and Immunological Research before the end of December 2001. Additionally, the German organization of patients suffering from Tourette syndrome (Tourette Society Germany) put a HTML version of the questionnaire online on its homepage.

The questionnaire consisted of 26 questions divided into six sections with additional free space for comments. The first part dealt with demographic data (age and sex), diagnosis, reason for cannabis use (therapeutically or recreationally), and experience with cannabis before the onset of disease. The second part dealt with the access to cannabis products, in-

cluding the reaction of the doctor to a request for treatment with THC and the reaction of the health insurance. Health insurance agencies in Germany are not obliged to pay for a treatment with THC, since there is no pharmaceutically-approved preparation in Germany. German doctors are allowed to prescribe Marinol®, a preparation of synthetically manufactured THC that is approved in the USA, and THC may also be bought by pharmacists from two German companies (THC Pharm and Delta 9 Pharma) to produce capsules or oily liquids for medical use according to formulas developed and issued by an institution of the German pharmacists association (N. N. Monographs 2001). It is up to the insurer whether to pay for a treatment or not. In Germany THC prescribed by a doctor is about ten times as expensive as THC in illegal cannabis products.

The remaining four parts of the questionnaire dealt with the kind of cannabis products used, the method of use, therapeutic effects and satisfaction, possible side effects, reasons for a possible change of dose, and a comparison between THC and natural cannabis preparations.

In all, 157 completed hard-copy questionnaires reached the Institute for Oncological and Immunological Research in Berlin or the Association for Cannabis as Medicine in Cologne. An additional 25 online questionnaires were sent to the ACM by the Tourette Society Germany. Of these 182 participants, 17 were excluded since they apparently did not suffer from severe conditions ("occasionally joint aches," "indigestion," etc.) or were apparently healthy (e.g., "prophylaxis against glaucoma"). Thus, 165 participants were included in the final analysis.

Many participants reported more than one diagnosis or symptom. Several diagnoses were given to describe the symptoms of the primary disease. For example, the diagnosis "multiple sclerosis" was supplemented by additional information, such as "spasticity" or "pain." Psychiatric problems, such as depression or sleeping disorder, were often added to the somatic primary disease. A maximum of three diagnoses were taken into account, with one primary diagnosis. This main diagnosis was either the primary disease or the assumed most severe disease.

The diagnoses were divided according to their most important symptoms into nine groups, pain, neurological, neuropsychiatric, gastrointestinal, glaucoma, asthma, immunological, psychiatric, and miscellaneous.

RESULTS

About two-thirds (61.2%) of the 165 participants included in the final analysis were male and 38.8% were female. Their median age was 40.3 ± 12.4 years (range: 16-87 years).

Of these, 142 participants reported prior experience with the medical use of cannabis products, while 22 had none. Fifty-three participants had asked their doctors to prescribe THC, of whom 40 did not receive THC because their doctor dismissed their request, or because the health insurance agency would not assume the costs. Sixteen participants had both experience with THC and natural cannabis products.

Sub-Group with No Medical Use

Twenty-two participants (11 men and 11 women) did not use cannabis products for therapeutic purposes. Nearly half of them (N = 10) suffered from Tourette syndrome and had completed an online questionnaire on the web site of the Tourette Society. Others suffered from pain, multiple sclerosis, spinal cord injury, glaucoma, cancer chemotherapy, and cancer.

Two had had experience with the recreational use of cannabis before the onset of their disease. Both reported of fear of criminal prosecution and had tried, in vain, to get THC from their doctor.

Fear of criminal prosecution was the main reason why cannabis had not been used in the group of non-users (N = 9). Other reasons are listed in Table 1. Among the additional reasons provided were: "I fear meeting the wrong people when buying cannabis." "I have not had any opportunity." "No studies available on safety of use." "Because of the costs." or "No serious supply with constant quality."

Sub-Group with Medical Use

About one-third of the 143 participants who reported medical use of cannabis were female (37.1%). Among the age groups below the age of 30, and among the 40 to 50 year olds, considerably more men than women used cannabis for medical reasons, while among the 30 to 40 year olds and the elder participants there was a more balanced sex distribution (Figure 1).

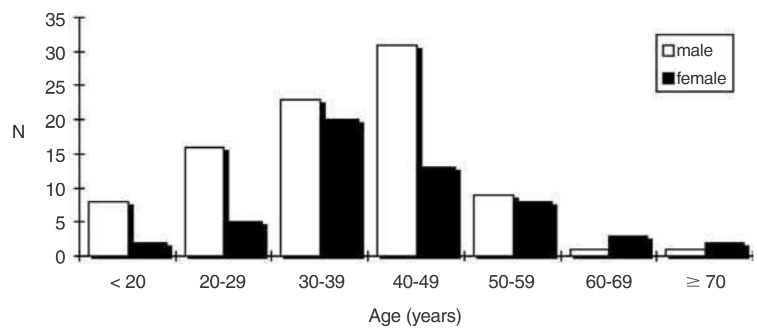
About half of the medical cannabis users (47.6%) had already had experience with the use of the drug before the onset of their disease.

One diagnosis was reported by 59.4%, two by 27.3% and three or more diagnoses by 13.3%. Among the primary diagnoses, we found a predominance of neurological symptoms or diseases (28.0%) and painful conditions (25.3%), followed by diseases with mainly gastrointestinal symptoms, such as nausea and appetite loss (14%). The most frequent

TABLE 1. Answers to the Question: Why Didn't You Use Cannabis Products Previously? (Multiple Answers Possible)

Given answers (N = 22)	**N**
I think that cannabis products do not help me.	1
I fear possible side effects.	1
I fear criminal procedures with use of natural cannabis products.	9
I think that my doctor will not prescribe dronabinol.	8
I have asked my doctor but he/she will not prescribe dronabinol to me.	5
My health insurance will not pay for the costs of dronabinol/Marinol.	4

FIGURE 1. Distribution of age according to gender (N = 143).



single diagnoses were multiple sclerosis (17.5%), Tourette syndrome (11.9%), HIV/AIDS (10.5%), migraine/headache (4.9%), chronic pain that was not more precisely described (4.2%), hepatitis C (3.5%), depression (2.8%), sleep disorders (2.8%), spinal cord injury (2.8%), back pain (2.8%), asthma (2.1%), allergy (2.1%), fibromyalgia (2.1%), menstrual pain (2.1%), and epilepsy (2.1%) (Table 2).

It is remarkable to note that many patients who used cannabis provided responses to a question that was only intended to be answered by participants who did not use the drug (Table 1). Some 21.7% said that they feared criminal involvement with use of natural cannabis products, 15.4% expressed their feeling that their doctor would not prescribe THC, and 9.1% answered that their doctor would not prescribe THC when they asked him. There was also some fear concerning discussion with doctors about self-medication with cannabis, expressed in their

TABLE 2. Primary or Main Diagnoses (N = 143)

Group	Diagnosis	N	%
Pain		36	25.2
	Arthritis	2	1.4
	Slipped disc	2	1.4
	Chronic pain	6	4.2
	Thalidomide consequences	1	0.7
	Fibromyalgia	3	2.1
	MCS (multiple chemical sensitivity)	1	0.7
	Menstrual pain	3	2.1
	Migraine/headache	7	4.9
	Werdnig-Hoffmann disease (spinal muscular atrophy)	1	0.7
	Neuralgia	1	0.7
	Neurofibromatosis	1	0.7
	Plexus damage	1	0.7
	Herpes zoster neuralgia	1	0.7
	Thalamic pain	1	0.7
	Gastric volvulus	1	0.7
	Lumbosacral back pain	4	2.8
Psychiatric		11	7.7
	Alcohol dependency	1	0.7
	Borderline syndrome	1	0.7
	Depression	4	2.8
	Drug dependency	1	0.7
	Sleep disorders	4	2.8
Neuropsychiatric		18	12.6
	Attention deficit disorder (ADD)	1	0.7
	Tourette syndrome	17	11.9
Neurological		40	28.0
	Borreliosis (Lyme disease)	2	1.4
	Epilepsy	3	2.1
	Friedreich's ataxia	1	0.7
	Multiple sclerosis	25	17.5
	Parkinson's disease	1	0.7
	Spinal cord injury	4	2.8
	Stroke	1	0.7
	Spasticity	1	0.7
	Spastic spinal paralysis	1	0.7
	Syringomyelia	1	0.7
Immunological		9	6.3
	Allergy	3	2.1
	Chronic bladder inflammation	1	0.7
	Crohn's disease	2	1.4
	Neurodermitis	1	0.7
	Rheumatism	2	1.4
Glaucoma		2	1.4
Gastrointestinal		20	14.0
	Hepatitis C	5	3.5
	HIV/AIDS	15	10.5

Group	Diagnosis	N	%
Asthma		3	2.1
Miscellaneous		4	2.8
	Alzheimer's disease	1	0.7
	Hypertension	1	0.7
	Cancer	1	0.7
	Menopausal discomfort	1	0.7

commentaries, e.g., "In my home town it is not possible to confide in the doctors."

In 82.5% (N = 118), natural cannabis products were used in the month before the survey. Eight had used THC/Marinol and two had employed both natural cannabis and THC in the previous month. Three did not indicate what they had used, and 12 who had experience with the medical use of cannabis products said that they did not use them in the previous month.

The main reasons cited for the use of natural cannabis products were preference of natural products (71.3%), having objections to request the doctor to prescribe THC (19.5%), refusal of the doctor to prescribe THC (10.5%), and refusal of the health insurance to pay the costs of a treatment with THC. There were many additional answers offered to this question, among them: "Ignorance of the doctor." "I grow my own." "I did not ask my doctor until now." "It is nonsense to manufacture synthetic THC," etc.

Fourteen participants made utilizable statements as their THC doses, which were 14.9 ± 9.5 mg on average, with a range from 4 to 35 mg (Figure 2), and 109 participants made utilizable statements on the dose of natural cannabis products (marijuana, hashish), which was 1.3 ± 0.9 grams on average (range: 0.02-3.5 g) (Figure 3).

The various products were inhaled by 55.9% of the medical cannabis or THC users, while 16.8% took them orally and 23.1% used both routes.

About three-quarters (74.8%) of the 143 individuals said that their disease was much improved by cannabis products. Additionally, 13.3% noted a small improvement and 2.1% noted no improvement, while 7.0% were unsure whether it improved their condition, and 2.8% did not respond to this question. The percentage of respondents who noted much improvement varied between 60 and 100% depending on diagnosis group (Figure 4).

More than half (54.5%), were very satisfied with the effects of the cannabis products they used, 28.0% were satisfied, 14.0% were partly

FIGURE 2. Daily doses of dronabinol (THC) (N = 14).

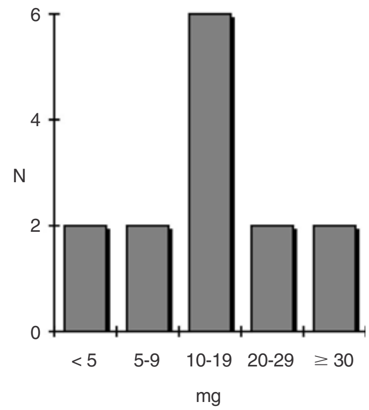
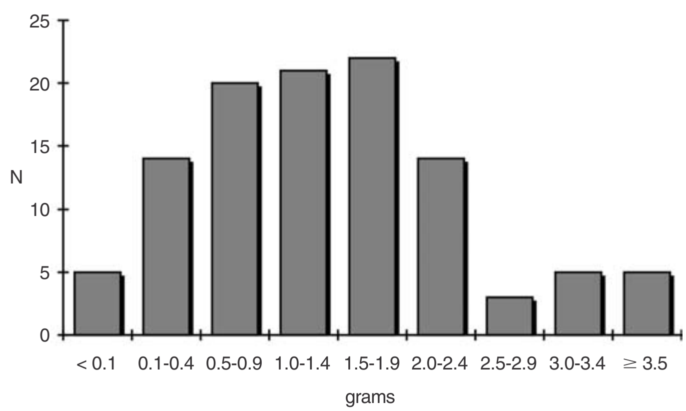


FIGURE 3. Daily doses of cannabis (N = 109).



satisfied, 2.1% were not satisfied, and 1.4% did not respond to this question (Figure 5).

More than two-thirds (69.2%) noted a significant improvement in their condition in comparison to other medical drugs, while 7.0% noted a small improvement and 2.8% no improvement, 17.5% said that they did not know or were not able to evaluate the amount of improvement, and 3.5% did not answer this question.

About three-quarters of participants (73.4%) answered “none” to the question on severity of side effects, while 22.4% reported that the side effects were “moderate” and 4.2% gave no answer (Figure 6).

FIGURE 4. Improvement of medical condition in dependency of disease group (N = 139). Number of respondents in diagnosis groups are given in parentheses. The bar representing "else" includes "little better," "not better," and "don't know." The 4 individuals with no answer were excluded from the graph.

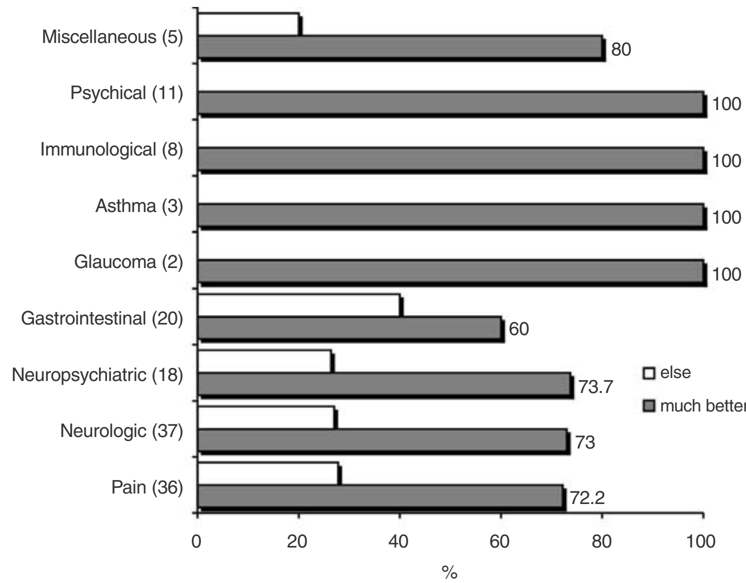
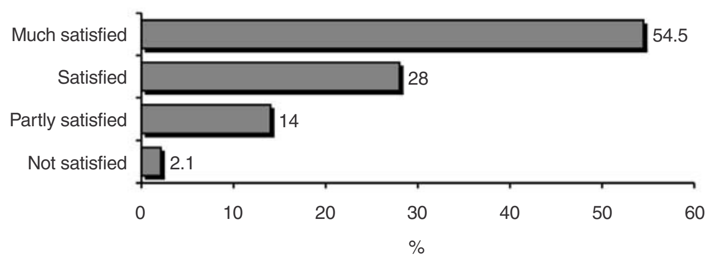


FIGURE 5. Satisfaction with cannabis products (N = 141).



Three-quarters (76.9%) reported no change in their dose during the previous three months, while 15.4% had reduced, and 3.5% had increased the dose. A few (4.2%) did not answer. The reason cited for dose increases was generally a reduced efficacy of the previous dose. One participant reported that he had stopped using opiates for pain therapy, and for this reason had increased the dose of cannabis. The main

reason for dose reduction (8.4%) was decrease in perceived disease severity. Among the written responses were: "Completely stopped, because of no positive effect." "Variation of quality." "Noted that a lower dose was equally effective." "Financial reasons." "Lack of money." "Reduced since blood pressure decreased heavily."

Three-quarters (75.5%) commented on results of discontinuation with regard to withdrawal symptoms. Of these 67.6% reported no withdrawal symptoms; in 17.6% these were mild, and in 2.8% they were more significant, while 12.0% reported that they could not evaluate the severity of withdrawal symptoms (Figure 7).

SUB-GROUP THAT REQUESTED THC

About one-third of the medical cannabis users (37.1%, N = 53) reported that they had asked their doctor to prescribe THC. In more than half of the cases the doctor was willing to do so, but in many instances the health insurer did not want to pay for the treatment. In 20.8%, THC was prescribed without difficulty. In an additional 28.3%, the doctor wished to prescribe THC, but the health insurance denied payment for

FIGURE 6. Severity of side effects (N = 137).

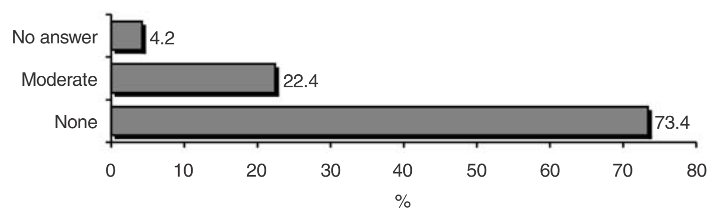
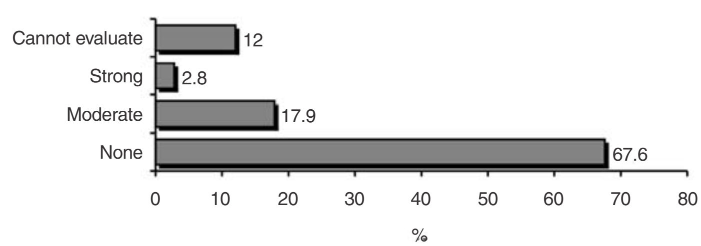


FIGURE 7. Severity of withdrawal (N = 108).



the treatment. In 3 cases (5.7%), the doctor was initially skeptical, but finally issued a prescription. In 37.7%, physicians refused and the patients did not receive a prescription. There was no answer in 4 cases (7.5%).

In some instances, the doctor's refusal to prescribe THC provoked further comments, ranging from the statement that the doctor was willing to issue a private prescription to a comment that the doctor got angry and wanted to escort the patient to the door. Among the responses were, "Doctor understood but did not react." "First doctor refused, second prescribed." "He refused and prescribed an opiate." "No experience with dronabinol." "Does not know the drug, thinks it is illegal."

Table 3 presents the reaction of the doctor according to the diagnosis. The range of diseases in which doctors were willing to prescribe THC was large. With multiple sclerosis, Tourette syndrome and a number of neurological syndromes, the willingness was high, in HIV/AIDS refusal and acceptance were equal.

More than half of the patients (31/53) who asked their doctor to prescribe THC made comments on the reaction of their health insurance. In 54.9%, the health insurance refused payment for a treatment. Table 4 presents the attitude of the health insurance according to the claimed condition.

Comparison of Natural Cannabis and THC

Sixteen participants reported experience with the medical use of THC as well as with natural cannabis products. Treatment tolerance was similar for both product groups, and there was a slight superiority in perceived efficacy for natural cannabis compared to THC/Marinol (Table 5). Side effects are compared in Table 6.

Sub-Group Without Prescription

A majority of participants (40/53) who solicited their doctor either failed to receive a prescription or a reimbursement of their treatment cost by health insurance. Six reported that they did not use cannabis products in the last month. Four had used THC (probably paid for on their own), 26 used natural cannabis products, and one had used both. Three did not respond to this question (Table 7).

TABLE 3. Willingness of the Doctor to Prescribe THC According to Diagnosis (N = 53)

Diagnosis	Willingness	Refusal	No answer	Total
Alzheimer's disease		1		1
Arthritis	1			1
Asthma		1	1	2
Attention deficit disorder (ADD)	1			1
Slipped disc	1			1
Borreliosis	1	1		2
Chronic pain		3		3
Depression	1		1	2
Epilepsy		1		1
Fibromyalgia	1			1
Friedreich's ataxia	1			1
Hepatitis C		1		1
HIV/AIDS	4	4	1	9
Menstrual pain		1		1
Migraine/headache	1			1
Multiple sclerosis	5	1	1	7
Neuralgia		1		1
Neurodermatitis		1		1
Plexus damage	1			1
Herpes zoster neuralgia		1		1
Spinal cord injury	1			1
Stroke	1			1
Spasticity	1			1
Spastic spinal paralysis	1			1
Syringomyelia	1			1
Thalamic pain	1			1
Tourette syndrome	5	2		7
Lumbosacral back pain		1		1
Total	29	20	4	53

Patient Advice to Lawmakers

All participants in the survey expressed advice to lawmakers with regard to cannabis legislation. Most (63.6%) marked two or more answers. General legalization of cannabis (74.1%) and legalization for medical use (e.g., by permission to cultivate the plant, 62.2%) received the greatest support (Table 8).

DISCUSSION

Fear of criminal sanctions with the use of illegal cannabis products, and the refusal of the doctor to prescribe THC, the pharmacologically

TABLE 4. Willingness of the Health Insurances to Pay for a Treatment with THC According to Diagnosis (N = 31)

Diagnosis	Agreed to pay	Refused to pay	Total
Asthma		1	1
Attention deficit disorder (ADD)		1	1
Slipped disc		1	1
Borreliosis	1		1
Fibromyalgia		1	1
Friedreich's ataxia		1	1
HIV/AIDS	2	2	4
Hepatitis C	1		1
Migraine/headache		1	1
Multiple sclerosis	3	2	5
Neuralgia		1	1
Plexus damage		1	1
Herpes zoster neuralgia		1	1
Spinal cord injury	1		1
Stroke		1	1
Spasticity	1		1
Spastic spinal paralysis		1	1
Syringomyelia	1		1
Thalamic pain	1		1
Tourette syndrome	3	1	4
Lumbosacral back pain		1	1
Total	14	17	31

TABLE 5. Answers to the Question: What Is Your General Impression of the Different Products with Regard to Effects on Your Disease?

Given answers (N = 16)	N	%
Cannabis and Marinol/dronabinol were about equally effective in my disease.	4	25.0
Cannabis was more effective than Marinol/dronabinol.	8	50.0
Marinol/dronabinol was more effective than cannabis.	3	18.8
No answer	1	6.3
Total	16	100.0

most active compound of cannabis, or the refusal of the health insurers to pay for a treatment with THC were the main reasons for not previously employing cannabis products in a small sub-group of the participants of this survey. The fear of criminal sanctions was also prevalent in the larger sub-group of patients who used cannabis medicinally. The illegal status of natural cannabis products seems to be a major problem in cases where legal products were not available to patients. Illegal use of

TABLE 6. Answers to the Question: What Is Your General Impression with Regard to a Comparison of Side Effects?

Given answers (N = 16)	N	%
Cannabis and Marinol/dronabinol had about equal side effects.	4	25.0
Cannabis had stronger side effects than Marinol/dronabinol.	5	31.3
Marinol/dronabinol had stronger side effects than cannabis.	4	25.0
No answer	3	18.8
Total	16	100.0

TABLE 7. Answers to the Question: Which Cannabis Products Did You Use Last Month?

Given answers (N = 40)	N	%
None	6	15.0
Natural cannabis products	26	65.0
Dronabinol	4	10.0
Cannabis + dronabinol	1	2.5
No answer	3	7.5
Total	40	100.0

TABLE 8. Answers to the Question: Which Advice Do You Have for Your Lawmaker with Regard to Regulation of the Access to Cannabis Products?

Given answers (N = 143)	N	%
I do not wish for change.	0	0.0
Natural cannabis products should be made available as medical drugs on a special prescription for narcotics.	25	17.5
Cannabis products should be made available on a normal prescription.	74	51.7
The medical use of cannabis products should be legalized (e.g., permission for cultivation for patients).	89	62.2
Cannabis should be legalized in general.	106	74.1

cannabis may result in criminal prosecution or fear thereof, a high price for an illegal drug, exposure to possible contamination, and other undesirable consequences (Grotenhermen 2002). Criminal sanctions must be regarded as one of the major side effects of medical cannabis use as long as it remains illegal.

The average age of 40 years in the medical cannabis users in this survey is high compared to recreational users in the general population.

The prevalence of recreational users in Germany is reported to be highest below the age of 30 (DHS 1998) or among young adults (EMCDDA 2001). This difference in age distribution between recreational and medical users can be explained by the different reasons and motivations for cannabis use. Chronic diseases for which cannabis products are used medicinally are more prevalent in older age groups.

The two main diagnosis groups among medical cannabis users were chronic pain and neurological disorders, and there was a wide range of medical conditions reflecting the multitude of drug effects that may be of therapeutic value, among them analgesia, muscle relaxation, anticonvulsant effects, appetite enhancement, anti-emesis, lowering of intraocular pressure, mood enhancement, sedation, anxiolytic properties, anti-inflammatory and anti-allergic effects, and bronchodilation. Often several diagnoses or symptoms were reported in which cannabis products were used.

Sometimes a combination of physical symptoms, e.g., pain and spasticity, were reported together with secondary psychiatric complaints, e.g., depression and sleeping disorders. These multifaceted effects on body and soul are well described in earlier surveys (TNO 1998, Barsch 1996, Consroe et al. 1997, Schnelle 1999) and clinical studies (Beal et al. 1995, Regelson et al. 1976). In a survey on the medical use of cannabis products among multiple sclerosis patients in the Netherlands, most patients reported that they used cannabis both for physical and psychic reasons (TNO 1998). In a survey among 106 AIDS patients in Germany 61.5% reported that they used the drug often or chronically "for general well-being," compared to 41.1% "against physical complaints" (Barsch 1996). In a survey by Consroe et al. (1997) in 92 MS patients, cannabis not only reduced spasticity, pain and tremor, but also anxiety and depression. Regelson et al. (1976), in their article on a clinical study with cancer patients, noted that THC was not only appetite, but also mood enhancing, an effect that was also found in a clinical study with AIDS patients twenty years later (Beal et al. 1995). According to some case reports, cannabis is even used successfully in endogenous depression (Grinspoon and Bakalar 1998), and in 2,480 patients interviewed by Mikuriya, mood disorders represented a major group of primary reasons for cannabis use, among them post-traumatic stress disorder, depression, dysthymia, bipolar syndrome and schizophrenia (Gieringer 2002).

The sedation of cannabis products is generally regarded as a side effect. For example, in a Californian study conducted in the 1980s that compared the efficacy of oral THC with smoked marijuana in patients

undergoing chemotherapy, 52% of patients who had employed marijuana and 64% of patients who had used oral THC reported symptoms of sedation (Musty and Rossi 2001). In a recent review of controlled clinical studies which had investigated the anti-emetic efficacy of cannabinoids, the authors noted "some potentially beneficial side effects" that occurred more often with cannabinoids than with other anti-emetics, namely "high," sedation or drowsiness and euphoria, and concluded: "In selected patients, the cannabinoids tested in these trials may be useful as mood enhancing adjuvants for controlling chemotherapy related sickness" (Tramèr et al. 2001, p. 16).

In its 1999 report the US Institute of Medicine also pointed to this combination therapy that may be gained by cannabinoid application and noted that "in cases where symptoms are multifaceted, the combination of THC effects might provide a form of adjunctive therapy; for example, AIDS wasting patients would likely benefit from a medication that simultaneously reduces anxiety, pain, and nausea while stimulating appetite" (Joy and Watson 1999).

Occasionally the subjective medical benefits of cannabis on physical symptoms are attributed to such psychological effects. In a trial of a cannabis user who suffered from hepatitis C, a professor for forensic toxicology was cited in a German newspaper as saying that although THC is used for some indications, among them glaucoma and AIDS, it was not an analgesic and that the user would only feel better and feel less pain due to the psychic effects (*Main Rheiner* of September 12, 2002).

In this survey physical complaints play the major role, and chronic pain accounts for about one quarter of the primary indications. With regard to the therapeutic physical effects of cannabis products, it appears that the quantitative distribution of indications in different surveys did not depend solely on the efficacy of the plant itself, since this distribution varied considerably, perhaps reflecting the knowledge of the therapeutic value of cannabis in certain patient groups (AIDS patients, MS patients). Thus, in the early 1990s Californian cannabis distribution centers (Cannabis Buyer's Clubs) showed a preponderance of people with AIDS. A 1993-1995 survey of 351 randomly-selected members of the San Francisco Cannabis Buyers Club found that 87% had a medically verified illness, of whom fully 84.5% were HIV positive (Brown et al. 1996). Only approximately 2% were diagnosed with multiple sclerosis or severe musculoskeletal disorders. Similarly 71% of the 739 members of the Los Angeles Cannabis Resource Center were HIV positive (Joy and Watson 1999).

In contrast, only 1.5% of the participants in an Australian survey stated that HIV/AIDS was their main reason to self-medicate with cannabis (Helliwell 1999), and in the UK the discussion on the medical use of cannabis has centered primarily around multiple sclerosis and chronic pain (House of Lords 1998). One reason might be the activities of the Alliance for Cannabis Therapeutics, founded by MS patients in 1992, spread the word of the benefits of cannabis among MS patients in that country. In the Australian survey, 51% of women said that they used the drug for premenstrual complaints and dysmenorrhea (Helliwell 1999), while in our survey only three participants used cannabis products for this indication. About 12% in this group used cannabis products to treat symptoms of Tourette syndrome, which is a rare diagnosis in other surveys, reflecting clinical research in this indication at the Medical School of Hannover, Germany, knowledge that quickly spread to the German self-help groups.

Such regional differences may also affect expert opinions. While the authors of the Institute of Medicine see "a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation" (Joy and Watson 1999), the report of the British House of Lords emphasized the use in multiple sclerosis (House of Lords 1998).

In recent years, there seems to be a world wide trend for a use of cannabis products in chronic pain and neurological disorders, which was also seen in changes in the membership profiles of Californian cannabis buyers clubs (Gieringer 2002). These indications are major foci of ongoing or planned clinical research with natural cannabis in the UK, Canada, and the US.

About 75% of the 143 individuals who used cannabis or THC medicinally in this survey said that their disease was much improved by cannabis products, and very few failed to note improvement. Satisfaction was high, with about 55% being very satisfied, and an additional 28% being somewhat satisfied. Side effects were usually regarded as infrequent, and withdrawal was generally not regarded as a major problem. However, it can be assumed that this is a highly selected group of medical cannabis users. Unsatisfied patients that found cannabis useless or experienced intolerable side effects and therefore stopped using it, are likely underrepresented. Therefore, this survey does not allow any conclusions on the percentage of patients who might benefit in unselected cohorts suffering from similar symptoms and diseases for which benefits were reported in this survey. It can be concluded, however, that cannabis products are very effective in at least some patients in a great

number of different conditions, in agreement with prior surveys, case reports and clinical studies in a wide range of indications.

Until recently, there have been very few representative surveys on the medical use of cannabis products, the largest being the survey of the Dutch institute TNO Preventie en Gezondheid among members of the Dutch Multiple Sclerosis Society (TNO 1998). About one-third of all members participated, of whom 13% reported use of cannabis at least once in their life, with 5% continuing its use. Since many ceased its employment, it could be assumed that a large percentage did not experience significant improvement of their condition, but there may have been additional reasons for stopping, e.g., the pressure of peers not to use a recreational drug. In the TNO survey, MS patients did not use cannabis more often than the general Dutch population. However, women above the age of 40 years were over-represented. In a more recent survey among 300 British MS patients presented at the 10th World Congress on Pain in 2002, the use rate was much higher. According to this investigation, about 45% of multiple sclerosis patients living in England used the drug, of whom 74% either eliminated or controlled spasticity, and 54% indicated that they used cannabis mainly for pain relief (*United Press International* of 18 August 2002). Patients who reported more severe symptoms were more likely to use cannabis than patients who had mild or moderate symptoms. The increasing number of patients using the drug may be due to a greater acceptance of medical cannabis among patients and the general population in several European countries.

Similar to the attitudes in the general population, doctors are divided on the issue. Skepticism applies not only to natural cannabis products (which remain illegal in Germany), but also to THC. There is ongoing scientific debate as to whether cannabis has medical value, or whether the benefits outweigh the side effects, e.g., in the *British Medical Journal* (Tramer et al. 2001, Campbell et al. 2001, Kalso 2001, Petro 2001, Iversen 2001, Grotenhermen 2001, Russo 2001), and in the *Journal of the German Medical Association* (Nedelmann 2000, Rommelspacher 2000, Flenker and Möller 2001). This controversy may influence the willingness of doctors to prescribe THC and their open mindedness to talk with their patients if they self-medicate with illegal cannabis preparations.

Results of this survey also show that German health insurers come to very different conclusions on the efficacy of a treatment with THC in many indications, resulting in contrasting attitudes towards reimburse-

ment. It seems that such decisions do not merely depend on the symptom or disease, i.e., medical considerations on the efficacy in a certain indication, but more on general attitudes about cannabis products, their medical usefulness and side effects.

In an Australian survey, 56% of patients said that they had talked to their doctor about their cannabis use while others hide this fact (Helliwell 1999). This may reflect fear that the doctor could condemn cannabis usage, resulting in a compromise of patient-doctor-relationship. In our first patient survey published in 1999 that included some questions to be answered by doctors only, only 11 doctors of the 128 participants (8.6%) responded (Schnelle 1999). We surmised that many patients did not dare to ask their doctor to participate in the survey, while others might have asked and were refused.

There is an ongoing debate as to the relative therapeutic value and side effects of whole plant preparations and isolated THC (dronabinol) (Grotenhermen 2002b), that is to say whether other compounds of the cannabis plant (other cannabinoids, terpenes, flavonoids, etc.) add to the primarily effects of THC (McPartland 2002, McPartland and Russo 2001). Only 16 participants in this survey had experience with both THC and natural cannabis (marijuana, hashish). This small number does not allow strong conclusions, as the results did not clearly favor one of the two alternatives. Side effects were regarded as similar for THC and natural cannabis, while efficacy was reported to be slightly superior for the whole plant. It is remarkable to note that both superiority of THC and superiority of cannabis were claimed by certain patients. Future research will help to give more definite answers to this question.

In conclusion, this survey adds to an increasing number of patient reports of successful and well-tolerated medical uses of cannabis products in a multitude of conditions, and provides some detailed information on dosing of THC and cannabis, methods of administration, or reasons for abstaining from such use. Since this is a selected group of patients with satisfied persons probably over-represented, no conclusions can be drawn with regard to experienced therapeutic and side effects in an unselected population. Furthermore, the results reflects the division of German doctors and health insurers on the issue, a division that does not seem to be based on medical considerations of efficacy for a certain indication, but more generally on attitudes towards cannabis products and their role in modern medicine.

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Attitudes and Beliefs About the Use of Cannabis for Symptom Control in a Palliative Population

Romayne Gallagher
J. Allan Best
Gillian Fyles
Pippa Hawley
Wendy Yeomans

ABSTRACT. There is increasing support for the use of cannabis in terminal illness. Sixty-eight patients from a palliative population were surveyed for their attitudes and beliefs about the use of cannabis in terminal illness.

Romayne Gallagher, MD, CCFP, is Acting Head, Division of Palliative Care, Department of Family Practice, UBC, Clinical Professor, Family Practice, UBC (E-mail: romayne@interchange.ubc.ca).

J. Allan Best, PhD, is Senior Scientist, Centre for Clinical Epidemiology and Evaluation, Vancouver Hospital and Health Sciences Centre, Clinical Professor, Health Care & Epidemiology, UBC (E-mail: abest@vanhosp.bc.ca).

Gillian Fyles, MD, is Medical Leader, Pain & Symptom Management/Palliative Care Program, Cancer Centre of Southern Interior, BC Cancer Agency, Clinical Instructor, Family Practice, UBC (E-mail: gfyles@bccancer.bc.ca).

Pippa Hawley, MD, FRCPC, FRACP, is Medical Leader, Pain & Symptom Management/Palliative Care Program, Vancouver Cancer Centre, BC Cancer Agency, Clinical Instructor, Department of Internal Medicine, UBC (E-mail: phawley@bccancer.bc.ca).

Wendy Yeomans, MD, Medical Manager, Palliative Care Program, Vancouver General Hospital, Clinical Instructor, Family Practice, UBC (E-mail: yeoman@interchange.ubc.ca).

Address correspondence to: Romayne Gallagher, Department of Family Practice, UBC, 5804 Fairview Avenue, Vancouver, BC, V6T 1Z3 Canada.

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Symptomatic patients with advanced illness were surveyed for attitudes, beliefs and symptom severity. Participants showed concern about cannabis' possible side effects and social consequences, with some significant differences between ethnic groups. Comfort with the use of cannabis for symptoms was reported by 80.9% and willingness to participate in a research study using cannabis was reported by 73.5%. Many felt cannabis was safer than morphine for pain management. Patients preferred an oral route of administration and had concerns about smoking cannabis.

Despite significant concerns about using cannabis, most palliative patients were still willing to try it for symptom relief. This may have implications if cannabis access regulations are relaxed, in that access will come before clinical studies on its uses and side effects in this population. If cannabis is viewed as safer than morphine by some, cannabis may be used as the sole analgesic and the standard therapy of opioids may be rejected. The reluctance of patients to smoke cannabis and the need for accurate information about cannabis and pain control in the palliative population is noted.

KEYWORDS. Cannabis, medical marijuana, palliative care, symptom relief

INTRODUCTION

There is increasing advocacy for the medical use of cannabis (Hoey 2001). There is biologic and clinical evidence to show that cannabis has efficacy in relieving pain, muscle spasm, nausea and anorexia (Joy et al. 1999). In humans, there is promising data regarding cancer pain (Noyes et al. 1975a; Noyes et al. 1975b; Staquet et al. 1978) and neuropathic pain (Pertwee 2002; Rice 2001). The effects of cannabinoids on these symptoms typically are modest and in most cases there are more effective medications, suggesting that cannabis' value will either be as an adjuvant medication, or in those who fail to respond adequately to standard medication.

As a pilot study for a our submission for a clinical trial of cannabis, we undertook to survey the palliative patient population for its willingness to try cannabis, to assess the population's knowledge about cannabis and its effects, and their knowledge about morphine for pain manage-

ment. We felt this would assist us in determining how willing that population was to trying the cannabis and what education they might need. Although numerous attitudinal studies have been done on various populations that smoke cannabis (Beesley and Russell 1997; Doblin and Kleiman 1991) none have been done on a palliative population.

METHODS

The survey consisted of 11 statements about cannabis, morphine and analgesics in general. The questions were drawn from perceived concerns about cannabis and from a previous study about knowledge and attitudes about palliative pain management in the general population (Gallagher 2001). Patients were asked if they would be willing to use cannabis for their symptoms as part of a study. Methods of taking cannabis were listed (smoking, pill, inhaler, sublingual drops, added to food, tea) and patients were asked to state their preference. The survey participants were asked to rate their pain, nausea, appetite and anxiety over the past two days using a visual analog scale of 0-10 (0 = no symptom, 10 = worst severity imaginable). In addition to the usual demographic information of age, gender, ethnicity, religion and education, patients were asked if they had used cannabis before and if they or a family member had a substance abuse disorder.

The survey was offered to patients who attended symptom management and palliative care clinics at two regional cancer centres, one in a major city (Vancouver, BC) and another in a smaller centre in the same province. As well, patients of inpatient palliative care programs in two Vancouver hospitals were asked to participate.

To be eligible, the patient must have an advanced life-limiting illness and been aware of their diagnosis. All the patients being seen at the cancer clinics and the palliative care units have exhausted any curative therapies and would now have therapy aimed at quality of life and comfort. The majority of patients are in their last six months of life. While almost all of the patients had a diagnosis of a malignancy, advanced cardiac, respiratory, liver or neurological diseases without dementia comprised the other diagnoses. A healthcare professional or family translator was used in those patients who could not read English fluently. Symptom scales were self-rated by patients and not by family or caregivers. Patients were excluded if they were delirious or had an impaired level of consciousness or were unable to give informed consent.

The study was approved by the university behavioral ethics committee. Frequency tables were prepared for each of the demographic variables and for each question. One-way analysis of variance was used to assess the effects of the demographic variables on each individual question.

RESULTS

A total of 68 surveys were analyzed. The mean age was 56.6 years with an age range of 29 to 92 with 5 missing entries. The gender ratio was 55.4% female and 44.6% male with 3 missing cases. Ethnicity of the study population showed 86% White of European origin, 7.7% Asian origin, 3.1% First Nations (Native North American), 1.5% Indo-Pakistani, and 1.5% other with 3 missing answers. The ethnicity of the whole province is 2.1% First Nations, 14.7% Asian and Indo-Pakistani, and 67.2% White of European origin (Statistics Canada 1996).

The study group education levels were 63.9% post-high school education, 23% high school and 13.1% less than high school and 7 missing entries. These education levels represent a slightly higher education than the provincial average, which is 52%, 29.5%, and 18%, respectively (Statistics Canada 1996). The majority of the study subjects were Christian (67.2%) with the next largest groups being other or none, both at 10.9% with 4 choosing not to answer. Cannabis had been used at some time in the past by 35.3% of the study group, 52.9% had not, with 8 participants not answering this question. A Canadian study from 1994 showed a general population use of cannabis of 7.6% of adults within the last year (Smart and Ogborne 2000), another Canadian self-report study showing that 1.9% of adults had used cannabis for medical use (self-defined) and that 6.8% used it recreationally within the previous year (Ogborne et al. 2000). A 1996 survey in the US found that 32% of people over the age of 12 had at some time tried cannabis (SAMHSA 1998). Four of the participants reported a history of substance abuse (6.6%) with 7 missing entries and 9 reported a family history of substance abuse (14.5%) with 6 missing entries.

The study population was asked to self-rate their intensity of pain, nausea, anorexia and anxiety. On a VAS scale, where 0 is absence of symptom and 10 is the worst symptom intensity imaginable, the mean pain score was 4.9. Aside from 7 missing cases, 45.9% rated it as a 6 or more denoting a significant degree of distress. The mean on the nausea scale was 2.87 and 7 cases not reporting, suggesting that most this popu-

lation was not experiencing significant nausea. However, 24.6% still rated their nausea at 6 or more out of 10. The anorexia scale had a mean of 3.97, with 8 not answering. Anorexia was reported at 6 or more by 28.3% of the study group. Anxiety reported by the study group was a mean of 3.54 with 9 unrecorded answers. The percentage of subjects reporting anxiety at 6 or more of 10 was 27.2%.

The responses to the statements about cannabis, its side effects and potential adverse social outcomes and statements about pain control are listed in Table 1.

Table 1 shows that there is a high number of "don't know" answers to the statements about cannabis and its use with a range of 17.6% for vulnerability to attack and theft, to a high of 36.8% for the statement that cannabis is safer than morphine. In addition some patients chose to not answer all the attitude and belief questions, with the highest level of missing answers for the questions about cannabis being safer than morphine (25/68). The question with the lowest rate of missing cases was the question about comfort with the use of medical cannabis, with only 6/68 participants not answering. Interestingly, 45.6% of the population agreed that "cannabis was safer than morphine" for the treatment of pain and other symptoms. Response to this question may have been influenced by the lead in statement that "cannabis is more natural than morphine." However, the other questions about risk of addiction with the use of morphine and loss of efficacy over time illustrated that the concern about morphine is not totally due to the wording. Participants were invited to write additional concerns about the use of medical cannabis and the majority of concerns were about side effects from smoked cannabis, permanent harm from its use and drug interactions.

Analysing the attitude and knowledge data with the demographics revealed no significant difference with age. Significantly more males were concerned about cannabis being addictive ($p = .031$), leading to the use of more harmful substances ($p = .036$), and causing an inability to think clearly ($p = .008$). These concerns were echoed when ethnicity (White of European origin vs. non-White) was considered. Non-Whites expressed significantly more concern over addiction ($p = .023$), inability to think clearly ($p = .004$), loss of effectiveness ($p = .042$) and leading to problems with the law ($p = .010$). Non-Whites also significantly disagreed with the statement about a low risk of addiction when treating pain with morphine ($p = .008$). Despite the high level of concern over the use of cannabis in non-Whites, there was no significant difference in the question of comfort with cannabis used for pain and ethnicity, as the vast majority of the non-Whites expressed comfort with its use. Non-

TABLE 1

Percent Frequencies of Attitude and Belief to Questions About Medical Cannabis and Pain Relief	***Strongly Agree***	***Agree***	***Disagree***	***Strongly Disagree***	***Don't know***	***Missing***
Cannabis used for the relief of pain or nausea is addictive.	0	22.1	26.5	23.5	27.9	19
Cannabis used for pain and nausea may lead to the use or abuse of harmful substances such as heroin.	2.9	13.2	36.8	27.9	19.1	13
If cannabis is used for the relief of pain and nausea it will cause an inability to think and act clearly.	1.5	23.5	35.3	7.4	32.4	22
Because cannabis is a more natural substance, it is safer than morphine and other strong pain killers.	10.3	35.3	14.7	2.9	36.8	25
Strong pain relievers should not be used to control pain early in the disease as the effectiveness of the medication will wear off and there will be poor pain control later on.	2.9	33.8	30.9	8.8	23.5	16
When using narcotics such as morphine for relieving pain, the risk of becoming addicted to the pain medication is extremely low.	10.3	39.7	14.7	11.8	23.5	16
The use of cannabis for medical reasons will cause disagreements and relationship problems between my loved ones and me.	0	7.4	38.2	33.8	20.6	14
The use of medical cannabis will cause problems with the law and I may be arrested or charged with possession of the substance.	5.9	29.4	23.5	11.8	29.4	20
The use of medical cannabis will make me vulnerable to attack and theft by substance abusers.	2.9	17.6	39.7	22.1	17.6	12
I would feel comfortable with the use of medical cannabis for the treatment of my pain and/or nausea.	33.8	47.1	5.9	4.4	8.8	6

Christians were significantly more concerned than Christians with cannabis leading to problems with the law (p = .035) and in their belief that cannabis was safer than morphine (p = .037). Those whose education level was high school or less were significantly less likely to believe that cannabis is safer than morphine (p = .014). Previous users of canna-

bis showed no significant differences in their beliefs or attitudes except to disagree more often with the statement that use of cannabis leads to addiction (p = .012). Those who agreed with the statement about comfort with cannabis' use in pain showed no significant difference from those who disagreed with its use, except for a significant concern over the use of cannabis causing relationship problems (p = .0004).

Despite the lack of knowledge about cannabis's possible side effects and concerns about social harms, there was overwhelming support for the use of cannabis for pain and/or nausea with 80.9% of the participants agreeing or strongly agreeing that they were comfortable with its use. Only 10.3% disagreed and 12 of 68 patients did not answer or replied, "don't know" to this question.

Participants were also asked "If you were offered an opportunity to take part in research assessing whether or not medical cannabis helps when added to your usual care, would you say yes or no?" Five of 68 patients (7.4%) did not answer this question, 73.5% said yes and 19.1% said no.

Patients were also asked to state their preference for route of administration. A number of participants chose to enter more than one preference so there were a total of 80 responses from 66 patients. Most patients were comfortable with an oral form, either as a pill (32), drops under tongue (15) or added to food (10). The smoking of cannabis was selected in only 12/80 responses. There were also several written concerns about the smoking of cannabis and harmful effects on the lung. Only 3/80 of responses agreed to "whatever works" suggesting that the route of administration remains a significant concern for patients, even those with significant symptoms.

DISCUSSION

The sample we obtained reflected the demographics of British Columbia quite closely. Utilization data from one of the units we drew our sample from showed their average age of 67, ten years younger than our sample (Tong et al. 1993). The difference is likely due to the outpatient cancer clinics where the younger and less frail patients attend.

The study numbers are small, which is a common difficulty of palliative care research, but they illustrate several key points. First, an overwhelming number of people are willing to participate in trials of medical cannabis and are comfortable with its use as a medication. The

support of the use of medical cannabis spans all demographics. The previous use of cannabis in our study population appears to have little or no bearing on willingness to use it as a medical therapy. Where they are getting their information was not known but may be helpful in future studies on cannabis beliefs and attitudes.

Currently, there is no consensus in the literature about which route of administration of cannabis is best for the various symptoms it is thought to help. Palliative patients in our study showed a definite preference for an oral form of medication. Only 15% of patients favoured smoking of cannabis, which should be a concern for clinical research studies using this form of cannabis. There are currently two oral preparations available, nabilone and dronabinol, but side effects from them are common and significant (Tramer et al. 2001) and it is reported by many patients that the smoked form works better for pain.

There are a number of significant differences in beliefs and attitudes towards cannabis especially when gender and ethnicity are considered. There were only 9 non-Whites who completed the study, so further research in the non-White population is necessary to confirm these results. Education about the use and effects of cannabis needs to be in multiple languages and focus on concerns that are common in the non-White ethnic groups.

There is significant literature about the risks and side effects of cannabis (Joy et al. 1999; Ogborne et al. 2000). Our population has a number of misconceptions about cannabis and its effects, but also about pain management and use of opioids. There needs to be a recognized and credible source of information for both patients and healthcare providers who are considering using or prescribing cannabis for symptom control. If cannabis is viewed as safer than morphine, the result may be the use of cannabis as the sole analgesic and the rejection of what is considered standard therapy for moderate to severe pain in a terminal illness.

Although our study population expresses significant concerns about the use of medical cannabis, most of this same population is still willing to try the cannabis for symptom control. This has implications for the consideration of releasing cannabis for a wider use among those with symptoms that may respond to cannabis therapy (Health Canada 2001). Currently, evidence for the efficacy of cannabis and its place in the management of symptoms in terminal illness is not clear and further research is necessary. Proposed cannabis access regulations in Canada and other countries will come into effect long before any clinical trials are complete. We are at risk for widespread use of cannabis before we

understand its uses in the palliative population. People who are facing the end of their life and whose symptoms are not well controlled are willing to trying anything that may hold out the hope of relief. They may also delay using standard pain and symptom therapy if they believe that cannabis is safer. It would be very helpful to know where cannabis works best in the palliative population based on clinical trials rather than word of mouth. We believe that there is a need for coordination between regulators and potential researchers to make the best use of this therapy based on scientific evidence.

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Guidelines for Cultivating Cannabis for Medicinal Purposes [Voorschriften voor de Verbouw van Cannabis voor Medicinale Doeleinden]

Annex to the Regulation of the Minister of Health, Welfare and Sport of 9 January 2003, GMT/BMC 2340685, containing policy guidelines for the decision on applications for Opium Act exemptions (Policy guidelines Opium Act exemptions) (authorised English translation)

1. Introduction
2. General
3. Personnel and Training
4. Buildings and Facilities
5. Equipment
6. Seeds and Propagation Material
7. Cultivation
8. Harvesting

Provided courtesy of: Willem K. Scholten, MSc, Pharm, MPA, Office of Medicinal Cannabis of the Pharmaceutical Affairs Directorate, Ministry of Health, Welfare and Sport, P.O. Box 20350, NL-2500 EJ The Hague, Netherlands (E-mail: wk.scholten@minvws.nl).

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1. INTRODUCTION

Under certain conditions, the Dutch government permits the cultivation of cannabis for medicinal purposes. In the case of herbal drugs, the cultivation method and primary processing of the plant determines the ultimate properties of the active pharmaceutical ingredient. Starting materials of herbal origin have a complex composition and can only be characterised to a limited extent through chemical or biological analysis. Therefore, an effective quality assurance system in the steps leading up to the production of the active pharmaceutical ingredient is needed in order to guarantee reproducible quality. These steps are cultivation, harvesting and primary processing.

The following guidelines for cultivating, harvesting and primary processing of cannabis constitute a quality assurance system that meets these requirements. The Office of Medicinal Cannabis (Bureau voor Medicinale Cannabis) will test on the basis of these requirements.

These guidelines have been derived from the general rules for Good Agricultural Practice of the Working Group on Herbal Medicinal Products of the European Medicines Evaluation Agency (EMEA).

This is an authorised translation of the official version in Dutch.

2. GENERAL

2.1 These guidelines apply to the cultivation, harvesting and primary processing of cannabis plants intended for medicinal use or the preparation of medicinal drugs. These guidelines must be read in connection with the European Good Manufacturing Practice (GMP) guidelines for active pharmaceutical products. They apply to all methods of production including organic cultivation. These guide-

lines also provide additional standards for the production and processing of herbal starting materials insofar as they identify the critical production steps that are needed to ensure good, reproducible quality.

2.2 The main objective of these guidelines is to increase the reliability of the medicines prepared from cannabis by establishing an appropriate quality standard for the herbal medicine cannabis. In particular, it is important that the cannabis:

- is produced hygienically to keep microbiological contamination to a minimum;
- is produced such that negative effects on the plants during cultivation, processing and storage are kept to a minimum;
- is produced under conditions that ensure that the therapeutic properties of the end product are constant and reproducible.

3. PERSONNEL AND TRAINING

3.1 Training

3.1.1 Personnel must have received adequate botanical/horticultural training before performing the tasks given to them.

3.1.2 Production personnel must be trained in the production techniques used.

3.1.3 Primary processing procedures must comply with the regulations on food hygiene.

3.2 Hygiene

3.2.1 All personnel entrusted with handling the herbal material must maintain proper personal hygiene.

3.2.2 Persons suffering from infectious diseases transmittable via food, including diarrhoea, or carriers of these diseases must be forbidden access to areas where they could come into contact with the herbal material.

3.2.3 Persons with open wounds, inflammations and skin-infections must be suspended from areas where they could come into contact with herbal material, unless they wear protective clothing or gloves until they have recovered completely.

3.2.4 Personnel must be protected from contact with toxic or potentially allergenic herbal material by means of adequate protective clothing.

4. BUILDINGS AND FACILITIES

4.1 Buildings used in the processing of harvested crops must be clean, well ventilated and must never be used for other activities.

4.2 Buildings must be designed in a manner that protects the crops against pests and domestic animals.

4.3 The medicinal cannabis must be stored:

- in a suitable packaging;
- in rooms with concrete or similar floors which are easy to clean;
- on pallets;
- at a sufficient distance from walls;
- well separated from other crops in order to prevent cross-contamination.

Organic products must be stored separately from products not grown organically.

4.4 Buildings where plant processing is carried out must have changing facilities, toilets and hand-washing facilities.

5. EQUIPMENT

5.1 Equipment used in plant cultivation and processing must be easy to clean in order to eliminate the risk of contamination.

5.2 Equipment and machinery should be mounted such that they are easily accessible. Machines used in fertiliser and pesticide application must be calibrated regularly.

5.3 The equipment must be made from materials other than wood. If wooden materials (such as pallets) are used, they must not come into direct contact with chemicals and contaminated materials, in order to prevent contamination of the herbal materials.

5.4 Equipment and machinery used for harvesting must be clean and in very good working condition. Machine parts that come into direct contact with the harvested crop must be cleaned regularly and must be free from oil and contamination, including residual plant matter.

6. SEEDS AND PROPAGATION MATERIAL

6.1 Seeds and propagation material must be botanically identified as to species, variety, chemotype and origin. The materials used must be traceable. Starting material must be free from pests and disease as much as possible in order to guarantee healthy growth.

6.2 Cuttings of female plants must be used as propagation material for the production of cannabis.

6.3 During the entire production process (cultivation, harvest, drying, packaging), the presence of male plants and different species, varieties or different plant parts must be monitored. Any impurities must be removed immediately.

7. CULTIVATION

7.1 Soil and fertilisation

7.1.1 Cannabis for medicinal purposes must not be grown on soil contaminated with sludge, heavy metals, pesticide residues or other chemicals. Any chemicals used must therefore be kept to the minimum effective dose.

7.1.2 Manure applied should be thoroughly composted and must be devoid of human faeces. Irrigation should be controlled and according to the needs of the cannabis plant. Fertilisers should be used in such a way that leaching is reduced to a minimum.

7.2 Irrigation

7.2.1 Irrigation must be controlled and only as required by the cannabis plant.

7.2.2 Irrigation water must contain as few as possible contaminants like faeces, heavy metals, herbicides, pesticides and toxicologically hazardous substances.

7.3 All tillage must be adapted to plant growth and requirements. Using herbicides and pesticides must be avoided as far as possible. Use and storage of pesticides must be in accordance with the recommendations of the manufacturer and the relevant approval authorities. Only qualified personnel are allowed to use such substances using only approved material but not in a period preceding the harvest, as indicated by the buyer or producer.

8. HARVESTING

8.1 Harvesting must be done when the plants have reached the best quality for the intended use.

8.2 Male, damaged, and dead plants must be removed.

8.3 Harvesting must take place under the best possible conditions, avoiding wet soil or extremely high air humidity. If harvesting occurs in wet conditions, additional care needs to be taken to avoid the adverse effects of moisture.

8.4 During harvesting, care must be taken that no other species or cannabis variety get mixed with the cannabis crop.

8.5 The harvested crop must not come into direct contact with the soil. Directly after harvesting, it must be prepared for transport in clean, dry conditions (e.g., sacks, baskets, boxes).

8.6 All containers must be clean and free from any residues from previous harvests; containers that are not in use must be kept in dry conditions, free of pests and inaccessible to domestic animals.

8.7 Mechanical damage and compacting of the herbal drug that could result in undesirable quality changes must be avoided. In this respect, take care to avoid:

- overfilling sacks/containers;
- stacking sacks/containers too high.

8.8 Freshly harvested herbal material must be delivered to the processing facility as quickly as possible in order to prevent thermal degradation.

8.9 The harvested crop must be protected from pests and domestic animals.

9. PRIMARY PROCESSING

9.1 Primary processing includes washing, cutting before drying, decontamination from pests, freezing, distillation, drying, etc.

9.2 On arrival at the processing facility, the harvested crop must be directly unloaded and unpacked. Prior to processing, the material must not be exposed to direct sunlight (except in cases that specifically require this) and must be protected from rain.

9.3 Drying

9.3.1 Drying crops directly on the ground or under direct sunlight must be avoided.

9.3.2 Uniform drying speed and prevention of mold growth must be assured.

9.3.3 In the case that plant material is dried in the open air, it must be spread in a thin layer. To ensure good air circulation the drying racks must be placed at sufficient distance to the floor.

9.3.4 In the case plant material is not dried in the open air optimal drying circumstances like temperature and drying time must be chosen.

9.4 Waste bins must be available and must be emptied and cleaned daily.

10. PACKAGING

10.1 Following repeated controls and removal of any sub-standard material or undesired objects, the product must be packaged in clean, dry and preferably new packaging. The label must be clear, firmly fixed and made from non-toxic material.

10.2 Reusable packaging material must be well cleaned and dried prior to use.

10.3 Packaging material must be stored in a clean, dry place that is free of pests and inaccessible to domestic animals. The packaging material must not contaminate the product.

11. STORAGE AND DISTRIBUTION

11.1 Dried, packaged products and extracts must be stored in a dry, well-ventilated building in which daily temperature fluctuations

are limited and good ventilation is ensured. Fresh products must be stored between 1°C and 5°C; frozen products must be kept at temperatures below −18°C (or below −20°C for long-term storage).

11.2 In the event of bulk transport, it is important to ensure dry conditions. To prevent mould formation or fermentation, it is advisable to use ventilated containers, transport vehicles and other ventilated facilities.

11.3 Decontamination of the storage area to combat pests must be carried out only where necessary and by authorised personnel only.

11.4 When frozen storage or saturated steam is used for pest control, the moisture content of the product must be controlled after treatment.

12. SPECIAL PROVISIONS FOR THE PRODUCTION OF CANNABIS INTENDED FOR PROCESSING INTO A STANDARDISED HERBAL DRUG

12.1 Herbs

12.1.1 In these guidelines, a herbal medicine is understood to mean any medicine that contains exclusively herbal drugs or herbal preparations as active ingredients.

12.1.2 Herbal drugs are plants or parts of plants in an unprocessed state which are used for medicinal or pharmaceutical purposes. A herbal drug or a preparation is regarded as one active substance in its entirety whether or not the constituents with therapeutic activity are known.

12.1.3 Herbal drug preparations are comminuted or powdered herbal drugs, extracts, tinctures, fatty or essential oils, expressed juices, processed resins or gums, etc., prepared from herbal drugs, and preparations that are produced through fractionation, purification or concentration.

12.1.4 In departure from the above, chemically defined isolated constituents or their mixtures are not considered herbal drug preparations.

12.1.5 Herbal drug preparations may contain other components such as solvents, diluents and preservatives.

12.2 If the cannabis is intended for processing into a standardised herbal medicine, the cannabis must be cultivated under such standardised conditions that the content of the constituents is constant. Protocols of the operations committed during the cultivation must be kept available.

12.3 The content of the main constituents, which includes Δ-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD), is determined quantitatively. For a selection of the other constituents, fingerprinting with a suitable technique, such as GC-MS, GC, HPLC or TLC will suffice.

12.4 Unless it is proven that omitting the standardisation of one of the following elements results in a constant and reproducible product, at least the following must be standardised during cultivation:

a. cultivar of the cannabis plant;
b. cultivation substrate;
c. day length;
d. light intensity;
e. colour temperature of the lighting;
f. atmospheric humidity;
g. temperature;
h. ventilation;
i. plant age at the time of harvesting;
j. time of day of harvesting.

12.5 Unless it is proven that omitting the standardisation of one of the following elements results in a constant and reproducible product, at least the following must be standardised during drying:

a. atmospheric humidity;
b. temperature;
c. ventilation;
d. drying time.

13. DOCUMENTATION

13.1 All processes and procedures which may affect the quality of the product must be recorded in the documentation for each batch. The following in particular must documented:

a. the location of cultivation and the name of the cultivator in charge;
b. details on crops previously grown at that location;
c. nature, origin and quantity of the herbal starting materials;
d. the chemicals and other substances used during cultivation, such as fertilisers, pesticides and herbicides;
e. standard cultivation conditions, if applicable;
f. particular circumstances which occurred during cultivation, harvesting and production which may affect the chemical composition, such as plant diseases or temporary departure from standard cultivation conditions, particularly during the harvesting period;
g. nature and quantity of the yield;
h. date or dates, and time or times of day when harvesting occurred;
i. drying conditions;
j. measures for pest control.

13.2 Analysis reports of soil analysis must be kept available in the dossier

13.3 Location

13.3.1 All batches originating from one location must be clearly labelled (e.g., with a batch number). This must be done as early on in the process as possible.

13.3.2 Batches originating from different geographic locations may only be combined if guaranteed to be the same, and that the mixture is homogenous. Mixing of batches must be documented.

13.3.3 It must be recorded in the documentation for each batch that the cultivation, harvest and primary processing procedures were in accordance with these requirements.

13.3.4 All parties involved in the production process must demand that their suppliers document all relevant stages and elements of the production process for each batch.

13.3.5 Audit results must be recorded in an audit report. The audit report and concomitant analysis reports and other documents must be kept for at least ten years.

14. SAFEGUARDING THE MATERIAL

14.1 The buildings in which the cannabis is cultivated, processed, packaged and stored must be sufficiently secured. This means that there must be security in force and that only authorised personnel is allowed access to the buildings.

14.2 The personnel involved in the production process of cannabis must be authorised for that purpose by the employer. When concluding the supply contract, the supplier designates authorised persons and indicates how this will be verified.

14.3 There must be a balanced administration of the cannabis.

14.4 Waste must be stored in such a way that theft is impossible. If waste is collected in bags it must be stored in a lockable container (for instance a pressing container) immediately.

ABSTRACTS

Cannabinoids and Pain Management Symposium: American Academy of Pain Management 13th Annual Clinical Meeting, September 28, 2002, Reno Hilton, Reno, NV, USA

Agenda:

08:00-09:00	John McPartland, DO: Progress in Neurobiology Related to Cannabinoids
09:05-10:05	Ethan Russo, MD: Cannabis: From Raw Plant to Pharmaceutical Products

10:05-10:20 Break

10:20-11:20	David Hadorn, MD, PhD: Trial Designs for Cannabinoids
11:25-12:25	William Notcutt, MD: Results from Cannabis-Based Medical Extract

12:25-1:55 Break

1:55-2:55	Mark Ware, MD: Canadian Cannabis: Grants, Trials and Outcomes
3:00-4:00	J. Hampton Atkinson, MD: University of California Center for Medicinal Cannabis Research (CMCR)
	David Hadorn, MD: Current and Planned Trials.

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PROGRESS IN NEUROBIOLOGY RELATED TO CANNABINOIDS. J.M. McPartland, MS, DO, Faculty of Health & Environmental Science, UNITEC, Private Bag 92025, Mt. Albert, Auckland, New Zealand.

Abstract: Elucidating the active ingredients in cannabis proved difficult. It took a dozen scientists, working from 1838 until 1964, to isolate and fully characterize tetrahydrocannabinol (THC) and cannabidiol (CBD). Since then, progress in neurobiology related to cannabinoids has accelerated. Analogs of THC were soon synthesized, many with greater potency and efficacy than the parent molecule. In 1988 a specific receptor for THC was demonstrated in the CNS, called CB_1. CB_1 is expressed in cells related to nociception and pain, such as afferent C-fibers, dorsal horn cells, periaqueductal gray area, rostral ventrolateral medulla, thalamus, amygdala, and cerebral cortex. The receptor-mediated effects of THC are primarily inhibitory, dampening the transmission of nociceptive signals mediated by glutamate and substance P. A second cannabinoid receptor (CB_2) was discovered in peripheral tissues, primarily in cells of immune function. CB_2 dampens inflammatory pain mediated by prostaglandins, leukotrienes, 15-HETE, nerve growth factor, tumor necrosis factor-alpha, and interleukin-1 beta. THC is highly lipophilic, so it also causes nonspecific, non-receptor mediated effects on cell membranes (e.g., the blood-brain barrier) and some enzyme systems (such as CYP-450s, COX, and LO enzymes). Furthermore, cannabis contains more than merely THC; other cannabinoids, terpenoids, and flavonoids contribute to the pharmacodynamics and pharmacokinetics of cannabis. Different cannabinoids cause different conformational changes in CB_1 and CB_2; these activate different G-proteins, such as Gi, Go, and Gs. This complicated scenario explains why different varieties of cannabis induce different types of cannabinomimetic effects.

In 1992, researchers discovered anandamide, the first of several endogenous cannabinoids (endocannabinoids). Anandamide provides analgesia, and is produced upon demand, via a calcium-dependent, "depolarization-induced suppression of excitation." After retrograde signaling of CB_1 receptors, anandamide undergoes re-uptake by a membrane transporter and degraded by the enzyme FAAH. Researchers are currently investigating anandamide reuptake inhibitors and FAAH inhibitors. Besides direct spinal effects, the cannabinoids also decrease pain by interacting with the descending antinociceptive (endorphin) path-

way. Lastly, cannabinoids inhibit the hypothalamus and amygdala, therefore extinguishing painful memory and fear conditioning, factors that turn chronic pain into human suffering.

CANNABIS: FROM RAW PLANT TO PHARMACEUTICAL PRODUCTS. Ethan Russo, MD, Montana Neurobehavioral Specialists, 900 North Orange St., Missoula, MT 59802, USA (E-mail: Erusso@blackfoot.net).

Abstract: Cannabis has a historical record as medicine for some 5000 years. This includes usage as a surgical anesthetic in Ancient China, among the Renaissance herbalists with hemp strains, and in more modern times with extracts of THC-predominant cannabis strains.

The biochemical bases for cannabis in pain management include its neuromodulatory roles on various neurotransmitter systems, its antioxidant and anti-inflammatory effects, and interactions with the endorphin system (Russo 2002).

The origin of cannabis' medicinal properties derives from glandular trichomes, where its therapeutic cannabinoids and terpenoids are produced. These, along with flavonoid components, combine in a synergistic fashion to promote analgesia and reduce adverse effects of THC (McPartland and Russo 2001).

Smoking of cannabis will likely never be an acceptable form of drug delivery to the FDA due to pulmonary sequelae and social ostracism, although some nations such as Canada and the Netherlands are allowing such prescription. Rather, the formulation of alternative delivery systems employing standardized preparations is most promising. Dose-metered inhalers of pure THC have produced pulmonary irritation in patients, but remain under development. Vaporization may represent a possible prescription alternative.

Oral administration, as with Marinol®, is hampered by first pass hepatic metabolism of THC to the more psychoactive 11-OH-THC, poor and irregular gastrointestinal absorption, and loss of the ability to titrate dosages toward symptom reduction.

The latter is problematic with rectal suppository forms, which are poorly accepted by American consumers.

To date, transdermal skin patch preparations have yielded only about 10% of the necessary absorption, and harbor a risk of diversion of used material that would still contain active medication.

In contrast, the program of GW Pharmaceuticals in the UK has been pursued with Home Office approval employing Good Agricultural Practice (GAP). Cannabis is grown organically in compost employing female clones from plants with known THC and CBD content. Fertilization is prevented to maximize production of cannabinoids in a climate-controlled indoor setting with Integrated Pest Management (IPM). Cannabis flowers are picked at senescense.

The strains are subjected to a supercritical carbon dioxide extraction at room temperature, retaining cannabinoids and terpenoids with little pigment. Waxy ballast is removed by "winterization" with ethanol. Resulting Cannabis-Based Medicine Extracts (CBME) are then placed in aerosol devices for oro-mucosal delivery in clinical trials (Whittle et al. 2001).

These formulations allow active effects in 40 minutes with the ability to titrate doses and with good patient acceptance. Additionally, an Advanced Delivery System (ADS) has been developed, which allows for security and control of dosing, with the option for remote monitoring by researchers or treating physicians.

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TRIAL DESIGNS FOR CANNABINOIDS. David Hadorn, GW Pharmaceuticals, Porton Down, Salisbury, England (E-mail: dhadorn@ fastmail.fm).

Abstract: Research studies testing the effectiveness of cannabinoids face several methodological challenges. Inclusion and exclusion criteria must be based primarily on anecdotal information due to the scarcity of controlled trials. GW Pharmaceuticals, a UK company developing a range of whole-cannabis extracts for prescription use, selected chronic neuropathic pain and multiple sclerosis as their initial indications for re-

search and development. Uncertainty exists concerning whether patients should be included in trials when they have not previously experienced cannabis or its effects; most authorities currently feel that doing so is acceptable. Another consideration is whether dosages should be standardized (e.g., the "Fulton puff procedure") as opposed to permitting patients to titrate dosage to a point of effect. Regulatory agencies generally expect standardized dosing, but the patient-controlled approach is more effective. Placebo controls are difficult to implement in cannabinoid research in view of the discernable "high" produced by THC. The extent to which placebo controls are needed outside of formal Phase III trials is controversial. Certain "active placebos," such as CBD, can be used in comparative studies of differing strain effects, or standard treatments can be used as the comparator. Cross-over studies are well-suited for cannabinoid research and are much more powerful statistically than parallel group studies. However, regulatory agencies devalue such studies because of (largely overblown) concerns about carry-over effects from one period to the next. N-of-1 trials are also very useful in cannabinoid research, particularly for establishing dose and dosage patterns, exploring routes of administration, monitoring safety and tolerability, and identifying valid and reliable outcome measures. Again, however, these trials are generally not accepted by regulatory authorities. The need for randomization outside formal Phase III trials is questionable; what is important is control of confounding variables, and despite prevailing dogma this can be accomplished without randomization. Outcome measures should include both condition-specific and generic indicators of health and quality of life.

RESULTS FROM TRIALS OF CANNABIS BASED MEDICAL EXTRACTS. William Notcutt, James Paget Hospital, Lowestoft Road, Great Yarmouth, Norfolk, NR31 6LA, UK.

Abstract: Cannabis Based Medicinal Extracts (CBME) derived from cloned plants and delivered sublingually are now available for clinical study in the UK. This was the first clinical program and its goals were to identify the therapeutic windows, to study the effects of CBME of varying constituent composition on patients suffering with chronic, refractory pain, to study safety and tolerability and to determine the approaches to more extensive and detailed studies.

Single patient studies were undertaken ("N of 1") as this was a new drug being used in heterogeneous group of patients with chronic, stable pain, poorly responsive to other treatment.

After a two-week assessment period the patients were started on a mixture of THC and CBD 1:1 for 2 weeks, open label. If they obtained benefits they went on to an eight-week randomized double-blind crossover placebo-controlled study. For 1 week periods they received either THC, CBD, THC:CBD or placebo. At the start of each week with a new extract, a supervised titration was undertaken.

A variety of assessments of pain, sleep, symptom control, depression, quality of life etc were undertaken. The results of these were used to determine whether patients had gained benefit. Those that did were able to go on to a long-term safety extension study.

Thirty-four patients were studied, 16 with MS, 8 with back pain post-spinal surgery and the remainder with a variety of mainly neuropathic problems, with a duration of pain between 1.5 and 36 years. Ages ranged from 26 to 66 years and 23 were women reflecting the patients with MS. Twelve had had some experience of cannabis for their symptoms and 7 had used it only on 1-2 occasions, often with adverse effects.

Two patients withdrew early due to inability cope with drug or the study. Seven patients who were frequent medicinal cannabis users received cannabinoid rescue medication to prevent them returning to their previous materials during placebo phases. Aggregated data from the remaining 25 patients demonstrates a fall in mean visual analogue scale (VAS) pain scores form 6 to 4 with both THC and THC:CBD mixture. CBD was of minimal benefit. There was a substantial improvement in sleep quality (15% → 55% of nights with good quality sleep) and the THC:CBD mixture was optimum. However, there was no significant increased duration of sleep. Depression scores fell and a Quality-of-Life assessment showed overall improvement.

The dose ranges showed a 25 and 30 fold (THC:CBD, THC) variation in daily consumption. The mean dose per day was 20 mg of THC alone or in the THC:CBD mixture.

Side effects were as anticipated. Drowsiness and dizziness were common during the initial uses of the extract but diminished as patients learned o titrate their drug more accurately. A similar outcome with euphoria ("high")/dysphoria was found. Dry mouth was the most common problem and some had a burning stinging sensation due to the spray itself. Panic was infrequent and hallucinations rare but neither were caused major distress. One vasovagal episode and 2 episodes of acute

dysphoria occurred early on during the acute dosing period and reflected a titration that was too rapid.

Of all 34 patients, 2 withdrew early and 4 received no benefit. Twenty had moderate or substantial clinical benefit. Twenty-eight patients continued into a long term extension study, yielding 42 patient years of experience with the extracts.

This first study has shown that the extract is effective and easily titrateable by the sublingual route, but that dosing is highly individual. Substantial benefit, particularly to sleep, can be obtained from THC and THC:CBD in patients for whom there is little else available. Side effects were anticipated, tolerable and manageable.

The way is now open for a wide range of high quality clinical research in this area.

CANADIAN CANNABIS: GRANTS, TRIALS AND OUTCOMES. Mark Ware, BA, MBBS, MRCP(UK), MSc, McGill University, Montreal (E-mail: Mware@total.net).

Abstract: There is a great deal of interest in the use of cannabis as a therapeutic agent, and good quality clinical research is needed to inform clinicians and policy makers in this heated debate. This talk presents results from preliminary studies of cannabis in pain management in Canada, including case reports, case series and prospective surveys, and summarizes existing research initiatives. The emphasis will be on raising awareness of practical issues and pitfalls in clinical cannabis research in Canada. An overview of the Health Canada Medical Marijuana Access Regulations will be included, which offers an opportunity for the long-term follow-up of medicinal cannabis users, particularly from a safety standpoint.

UNIVERSITY OF CALIFORNIA CENTER FOR MEDICINAL CANNABIS RESEARCH (CMCR). J. Hampton Atkinson, University of California San Diego (E-mail: jhatkinson@ucsd.edu).

Abstract: The Center for Medicinal Cannabis Research (CMCR) was established at the University of California in August 2000, with the overarching objective of conducting high quality scientific studies to ascertain the general medical safety and efficacy of cannabis products

and examine alternative forms of cannabis administration. Further the CMCR was intended to be a model resource for health policy planning by virtue of its close collaboration with federal, state, and academic entities. To date the CMCR has successfully released 3 calls for proposals to California investigators at private and state-funded academic and related institutions. Submitted proposals are evaluated for scientific merit by a national panel of experts; approved studies are forwarded for state and federal regulatory review. Seven clinical and pre-clinical studies have been approved overall, funded, and are in progress; 3 studies have received scientific and regulatory approval and are due to commence; 5 additional studies are undergoing state and federal review. Clinical studies in progress or forthcoming address efficacy of cannabis as analgesic for painful disorders due to HIV or cancer and as therapy for spasticity in multiple sclerosis and for nausea due to chemotherapy; related studies evaluate safety of cannabis; pre-clinical models intend to evaluate mechanisms of analgesia. A collegial working relationship with state and federal agencies, including the Drug Enforcement Agency, Food and Drug Administration, and National Institute on Drug Abuse, has developed.

CURRENT AND PLANNED TRIALS–GW PHARMACEUTICALS.
David Hadorn, GW Pharmaceuticals, Porton Down, Salisbury, England (E-mail: dhadorn@fastmail.fm).

Abstract: GW Pharmaceuticals is a UK-based company developing a range of whole-cannabis extracts for prescription use. The company's initial indications for study, multiple sclerosis and neuropathic pain, were selected from a wealth of anecdotal information, animal studies, and limited data from controlled trials. Four Phase III trials on these indications are nearing completion, with several more specific trials in these areas underway, including bladder dysfunction in multiple sclerosis, neuropathic pain and sleep, and patients with spinal cord injury, allodynia, or brachial plexus avulsion. Cancer pain is being studied in a Phase III trial and a Phase II trial has begun in peri-operative pain. Initial work is also underway in rheumatoid arthritis and inflammatory bowel disease, glaucoma, cystic fibrosis, insomnia, and schizophrenia. Study preparations are whole-plant extracts, with principal cannabinoids being THC, CBD, or a 1:1 mixture of both THC and CBD. A pump ac-

tion oral spray delivers 2.5 mg of either or both cannabinoids per actuation. Initial dosing is performed in the clinic under medical supervision, followed by self-titration at home. Findings from Phase II studies showed that patients experienced relief of neuropathic pain, improvement in spasticity, bladder-related symptoms, and in sleep, mood and overall sense of well-being. An opiate-sparing effect was also observed in patients taking opiates for pain. Of the first 109 refractory patients enrolled in Phase II trials, 88 completed the acute phase, of which 86 elected to continue long term. Safety evaluation incorporating 250 patient-years of exposure revealed the extracts to be generally well tolerated, with a predictable pattern of generally mild adverse events. No evidence of tolerance was observed.

BOOK REVIEW

BIOLOGY OF MARIJUANA: FROM GENE TO BEHAVIOUR. Onaivi, Emmanuel S. (Editor). *London: Taylor and Francis, 2002, 635 pp., $150, hardcover.*

"The truth is rarely clear and never simple" Oscar Wilde

The number of new books, reviews and dedicated journal issues on cannabis and cannabinoids being published in the last few years is remarkable. The perspectives from which cannabis may be approached range from the macro- (e.g., public health, legal and political) level down to micro- (molecular and neurophysiological) level, with a multitude of positions in between. Any new book on cannabis must be assessed, therefore, with these dimensions in mind.

Choosing an editorial path through the modern cannabinoid landscape is not a matter for the faint of heart. Clear and succinct reviews should serve as signposts for the future of cannabis research. For example, the 1999 report from the Institute of Medicine carefully reviewed the existing research with a view to assessing the therapeutic potential of cannabis, while Zimmer and Morgan's *Marijuana Myths, Marijuana Facts* opted for a more critical interpretation of the literature. Whatever the approach, a new publication must carefully describe its aims and intended audience to avoid losing relevance as a reference tool.

With the publication of *Biology of Marijuana: From Gene to Behaviour*, Emmanuel Onaivi has produced an addition to the cannabinoid bookshelf which is full of detail, but which lacks sufficient overall structure and coherence to give it any real merit as a unified work. It is perhaps

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unfortunate that this textbook arrived for review at the same time as the publication of an issue of a specialty journal dedicated to endocannabinoids (*Prostaglandins Leukot Essent Fatty Acids* 2002;66(2/3)). This issue presented reviews of the most up-to-date research in this area, written by many of the same outstanding authors that have contributed to Onaivi's book, with a clear focus and solid framework for reference. A further difficulty is that textbooks are notoriously out of date by the time they come to press, and as a result there are no references in *Biology of Marijuana* published later than 2000. This reduces the books value as a reference tool.

The choice of title is unfortunate, as it is really not strictly about the biology of marijuana; it is a collection of reviews of various aspects of the scientific cannabinoid literature, and at times the text wanders far from the cannabis plant itself. As a whole the book is not well organized. The organization of the material does not follow any clear logic. The topics jump randomly from molecular studies to clinical effects and back again, with no clear pattern emerging to tie them all together. The individual contributions are, for the most part, well written and balanced and provide some useful perspectives on cannabinoid pharmacology. The list of authors includes internationally recognized experts on the areas involved. Chapters of particular relevance to clinicians include Sañudo-Pena and Fride on movement disorders, Solowij on cognitive function, and Murphy on endocrine function; while the chapters by Glass and McAllister on cannabinoid mediated signal transduction and Onaivi and others on cannabinoid receptor genetics are detailed and useful overviews. The last chapter by Hubbbard on adverse events, however, does not contribute meaningfully to the overall work, as it draws substantially from other reviews of adverse effects. Readers are better advised to stick to the relevant chapters rather than rely on this rather scant handling at the end of the book.

In summary, Onaivi has taken on a work that is timely as we enter a second decade of exciting progress in the neurobiology of cannabinoids. It joins an expanding collection of reviews of this literature, and will be a useful source of reference to clinicians and scientists. Reviews must acknowledge their limitations, and real scholars should always go to the primary references to support the assumptions on which to base their hypotheses and arguments.

Mark Ware, MD
Departments of Family Medicine and Anaesthesia
McGill University
Montreal, Quebec, Canada

Introduction:
Cannabis:
From Pariah to Prescription

Ethan Russo

SUMMARY. Cannabis has been employed in human medicine for more than 4000 years. In the last century, political prohibition led to its disappearance from the conventional pharmacopoeia, but this trend is reversing due to the broad acceptance and application of this forbidden medicine by patients with chronic and intractable disorders inadequately treated by available therapeutics. This study addresses the "road back" for cannabis medicines, and reacceptance as prescription products.

Current pharmacology of the two primary therapeutic phytocannabinoids, THC and CBD, is reviewed with respect to herbal synergy and as pertains to treatment of pain, spasm and the wide range of therapeutic applications and adverse effects of cannabis.

In particular, the efforts of GW Pharmaceuticals to develop cannabis based medicine extracts (CBME) are documented including cultivation of genetically-selected medical-grade cannabis cloned strains in glass houses with organic and integrated pest management techniques, and their processing employing supercritical carbon dioxide extraction and winterization. These CBMEs are then available for formulation of dos-

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Ethan Russo, MD, is a Clinical Child and Adult Neurologist, Clinical Assistant Professor of Medicine, University of Washington, and Adjunct Associate Professor of Pharmacy, University of Montana, 2235 Wylie Avenue, Missoula, MT 59802 USA (E-mail: erusso@montanadsl.net).

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age forms including sublingual extracts and inhaled forms. An optional Advanced Delivery System (ADS) is also discussed.

KEYWORDS. Medical marijuana, cannabis, THC, cannabidiol, herbal treatment, alternative delivery systems, psychopharmacology

The *Journal of Cannabis Therapeutics* is pleased to mark with this the publication the transition of cannabis from a forbidden herb back into the realm of prescription medicine. Although a recognized and documented therapeutic agent for more than 4000 years (Aldrich 1997; Russo 2003; Russo 2001), cannabis became politicized in the early 20th century, leading to its ultimate prohibition in most industrialized nations. Cannabis was dropped from the *National Formulary* in the USA in 1941, and the *British Pharmacopoeia* in 1971. Reasons for the loss of cannabis as an available pharmaceutical were complex, related to a perceived risk of abuse, but also included formidable quality control issues such as lack of reliable or consistent supplies from India, idiosyncratic variability of patient responses to available preparations, and the advent of modern single product pharmacotherapy. The road back for cannabis medicines, as it were, has been a difficult and circuitous journey, beset by politics to a greater extent than science.

The essential features that characterize a prescription medicine require it to be of proven quality, consistency, clinical efficacy, and safety. For the last thirty-plus years, 85% of the world's research dollars for cannabis have been provided by the National Institute on Drug Abuse (NIDA), whose orientation has certainly not tended towards proof of therapeutic efficacy for this ancient herb. The lead has thus been taken by Europeans, whose medicine has never strayed quite so far from the realm of vegetable *materia medica*. Our account will document the progress of GW Pharmaceuticals, which, with full backing of the UK Home Office, has achieved the feat in five years of progressing from the idea of restoring cannabis to the pharmacy, all the way through to submission of a lead product for regulatory approval by the Medicines and Healthcare Products Regulatory Agency (MHRA, formerly the Medicines Control Agency).

As previously published two years ago (Whittle, Guy, and Robson 2001), many hurdles exist when considering the concept of how to produce a prescription cannabis product (p. 186):

- the concept of cannabis-based medicines as botanicals as opposed to pure cannabinoids;
- selective breeding of high yielding chemovars that produce an abundance of one particular cannabinoid;
- investigation of the pharmacological properties of various cannabinoids, i.e., cannabis is not just THC;
- variability of composition of cannabis. The geographical and genetic basis for variation in cannabinoid content of cannabis biomass and its control to give a standardised product;
- the quality aspects of cannabis biomass production;
- routes of administration and optimisation of formulations to achieve particular pharmacokinetic profiles;
- regulatory issues, including health registration, and international legal requirements;
- security packaging and anti-diversionary devices which can be used in connection with cannabis-based medicines in order to satisfy statutory requirements.

As is evident, the process of preparing a botanical for approval as medicine is comparable, but yet more complex than that for the New Chemical Entity (NCE), or novel synthetic pharmaceutical. A formidable barrier remains in the assignation and perception of cannabis as a drug of abuse. In the USA, cannabis was placed in the most restrictive category, Schedule I of the Controlled Substances Act in 1970, which encompasses drugs that are dangerous and addictive and lack recognized medical utility. It requires emphasis that this assignment was political and designed as a temporary, pending reassignment by the Shaffer Commission in 1972 (Abuse 1972). President Nixon rejected their recommendations of medical access and decriminalization before even reading the final report. Additionally, Schedule I assignation remains anachronistic (Haines et al. 2000). Many such drugs, including cannabis and LSD have had clear therapeutic indications in the past. Others, such as diamorphine (heroin), are forbidden in the USA, but retain legal pharmaceutical status in the UK. At least, controversy about such blanket proscriptions exists, and certainly with advancing knowledge, debate and reconsideration are required. A detailed analysis of the complexities of the cannabis question in the UK is available (Whittle and Guy

2003). The same publication outlines scientific evidence that cannabis based medicine extracts (CBME) may offer a distinct advantage over THC alone (Marinol®):

1. *Potentiation*. Based on a concept noted for endocannabinoids and their precursors called the "entourage effect" (Ben-Shabat et al. 1998; Mechoulam and Ben-Shabat 1999), various phytocannabinoid components, whether active (CBD, CBC) or relatively inactive (CBN) affect the cannabinoid receptor binding, pharmacokinetics and metabolism of THC. The same may be true of non-cannabinoid components, such as the essential oil terpenoids (McPartland and Russo 2001; Russo and McPartland 2003).
2. *Antagonism*. Cannabidiol mitigates side effects of THC (Karniol et al. 1975; Mechoulam, Parker, and Gallily 2002), including its intoxication liability. Additionally, other cannabis components may be helpful in this regard, e.g., terpenoids such as pulegone, 1, 8-cineole, and α-pinene may counter the short-term memory impairment engendered by THC (McPartland and Russo 2001; Russo and McPartland 2003).
3. *Summation*. A number of cannabis components may contribute to a certain therapeutic effect of THC (Williamson and Evans 2000; McPartland and Russo 2001).
4. *Pharmacokinetic*. For example, CBD alters the metabolism of THC by inhibiting its hepatic conversion to 11-OH-THC (Zuardi et al. 1982).
5. *Metabolism*. Whittle and Guy (2003) argue, as have others (Tyler 1994; Russo 2001) that due to co-evolution over the millennia, humans are better able to metabolize herbal preparations (i.e., cannabis) as compared to synthetic pharmaceuticals (i.e., synthetic cannabinoids).

Beyond the issues of regulation and rationale, the next step is to grow the plant. *Cannabis sativa*, despite its cosmopolitan propagation on the planet, is a rather exacting species insofar as optimal production of desirable medicinal cannabinoids is concerned. Such production is greatest in unfertilized female flowering tops, most commonly known as *sinsemilla* (Spanish, "without seed"), or *ganja*, the Sanskrit term for a process known in India for some 2500 years (Figure 1). THC production is increased by selecting certain strains and exposing them to ultraviolet light (Pate 1994). In the organization of the primary GW Pharmaceuticals production glasshouse, David Potter and Etienne de

FIGURE 1. Unfertilized female cannabis flower (photograph courtesy of GW Pharmaceuticals).

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Meijer have outlined additional important factors (Potter 2003; de Meijer 2003): high yield per area, high cannabinoid purity, high inflorescence to leaf ratio ("harvest index"), avoidance of diseases and pests, production of sturdy growth conducive to subsequent processing and ease of harvest.

Consistency is achieved by clonal propagation of cuttings from select strains called "mother plants," that yield shorter specimens with less waste stem material. Successful propagation occurs with 95% of cuttings (Figure 2).

A decision was made to produce different cannabinoid ratios for prescription CBMEs, through the use of separate high-THC and high-CBD strains, or their combination in a fixed-ratio. This work was initiated by HortaPharm B.V. a generation ago in Holland, and selected strains were developed there, and the seeds imported into the UK in 1998 (de Meijer 2003). The high-THC strain was originally produced by hybridization of ((Afghani × Mexican) × Colombian) genetics, said to be reminiscent of the commercial (if illegal) "Skunk #1" strain (Potter 2003). An initial 400 plants grown from seed were analyzed for cannabinoid concentration and purity, leading to five chemovars ("chemical varieties" or phenotypes) that were selected for commercial cultivation potential. A high-CBD strain was similarly selected from 1600 seeds yielding a selection of the best four chemovars. It has been determined that cannabis

FIGURE 2. Clonal growth in glasshouse (photograph courtesy of GW Pharmaceuticals).

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plant vigor, architecture, and glandular trichome density and metabolic efficiency in cannabinoid production are all polygenetically-determined traits, but affected by environmental factors (de Meijer 2003; de Meijer et al. 2003). Together, they determine the "cannabinoid quality." The chemovar is the primary determinant, however, of what cannabinoid ratios result. Additional line selection via repetitive self-fertilization has also been employed to maximize appropriate selection of both parents of a hybrid (de Meijer 2003).

In this particular instance, GW Pharmaceuticals chose to produce separate chemovars that selectively yield THC, CBD and THCV (83% theoretical maximum), CBC (76% theoretical maximum) or even CBG in relatively high amounts (de Meijer 2003). Although genetic modification (GM) of cannabis has often been discussed in certain quarters, it is abundantly clear from the above discussion that tremendous variation of chemical parameters is readily available with application of standard Mendelian genetic breeding techniques, and there is no rational reason for adding to the cannabis controversy by rendering it a genetically-modified organism (GMO).

As cannabis propagation and quality are subject to the vagaries of weather, all the more in a cloudy and wet northern clime, artificial light-

ing under glass was deemed the preferred method for pharmaceutical production in the UK. Mother plants are grown under high-pressure sodium (HPS) lights continuously at 75 watts/m^2 PAR (Photosythetically Active Radiation) (equivalent to 31,000 lux of natural sunlight) at 25°C in an organic compost ("leaf mould") to a height of 2 m, allowing pruning and the production of as many as 80 more cuttings for propagation (Potter 2003). The mother plant may be utilized for two or more "flushes" over the next few months before its vigor diminishes.

Clones are placed in peat pots after treatment with rooting hormone, trimming to retain one axial bud, and are grown out in polythene tunnels under high humidity with 24 hour light for two weeks until "potting up" (Potter 2003). Plants are continued under perpetual illumination for about three weeks until attaining a height of 50 cm, before shifting to a 12-hour light/12-hour dark critical day-length regimen to induce flowering.

All cultivation is performed in accord with Good Agricultural Practice (GAP) methods of the European Medicines Evaluation Agency in conjunction with rules of the UK Medicines Control Agency (Medicines Control 1997) for the production of a Botanical Drug Substance (BDS). [For the approved process of medicinal cannabis cultivation in the Netherlands, see the article in a prior issue of *Journal of Cannabis Therapeutics* (Anonymous 2003)]. Microbiological safety is crucial, and is a monitored function by regulatory agencies. In this instance GW Pharmaceuticals chose to use some minimal mineral sources of soil enrichment to avoid possible pathogen exposure from organic sources (Potter 2003). However, no pesticides whatsoever have been employed. Common pests are kept at bay by positive pressure in the glasshouses, and utilization of integrated pest management (IPM). Pests of concern have included spider mites (*Tetanychus* spp.) and onion (tobacco) thrips (*Thrips tabaci*). These are controlled through release of predatory mites, and kept at low level. For a comprehensive examination of the topic, the reader is urged to consult the superb *Hemp diseases and pests: Management and biological control* (McPartland, Clarke, and Watson 2000).

Fungal issues to date at the GW facilities have mainly pertained to grey mold (*Botrytis cinerea*) and powdery mildew (*Sphaerotheca macularis*). Control is achieved mainly by avoidance of high humidity close to time of harvest for the former, and increasing light pressure while avoiding excessive nitrogen exposure for the latter. When diseased plants do arise, affected specimens are destroyed.

While trials of outdoor cultivation were attempted with CBD-rich strains, daunting problems were encountered in the cool, damp British climate (Potter 2003).

Because cannabigerol (CBG) levels are dependent upon plant maturity, both the THC- and CBD-rich chemovars are harvested at the same growth stage at the onset of senescence, at which time the flowering tops representing 90% of the weight of the plants' aerial portions. Drying under a stream of dehumidified air from 25 down to 12% moisture content is then achieved under dark conditions to minimize cannabinoid oxidation (Whittle, Guy, and Robson 2001). The resultant mixture of dried unfertilized flowers, stalks and leaves yields 15% THC or 8% CBD in the respective chemovars (Figures 3, 4, and 5).

Interestingly, in the "raw" state, much of the THC and CBD are in the form of cannabinoid acids, THCA and CBDA, which are low in cannabinoid pharmacological activity. It is only after decarboxylation by progressive oxidation over time, after heating, or in the extraction process, that significant THC and CBD levels are produced and pharmacological benefits are obtained.

FIGURE 3. High CBD strain in GW Pharmaceuticals glasshouse (photograph courtesy of David Downs, PhD, GW Pharmaceuticals).

FIGURE 4. High THC strain in GW Pharmaceuticals glasshouse (photograph courtesy of David Downs, PhD, GW Pharmaceuticals).

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Historically, cannabis extracts were ethanol-based, dating back to the experiments of O'Shaughnessy in India in the 19th century (O'Shaughnessy 1838-1840). GW Pharmaceuticals has opted for a more modern technique employing supercritical CO_2 extraction (Whittle, Guy, and Robson 2001). This has distinct advantages, as organic materials are extracted at approximately body temperature with retention of essential oil terpenoid components that seemingly contribute to medicinal effects of cannabis (McPartland and Russo 2001). Additionally, no solvent residue remains after the process. Although such extraction does include some waxy ballast, this is easily removed by "winterization," or chilling in an ethanol solution. The resultant liquid CBME is then ready for pharmaceutical preparation.

Whereas oral ingestion and smoking have been favored methods of application in the past, they are not likely to be the primary modes of administration in the future of clinical cannabis as a prescription medicine. Oral administration, such as with Marinol® (synthetic THC, or "dronabinol" in sesame oil) was introduced into the USA market in

FIGURE 5. Dried cannabis ready for processing (photograph courtesy of GW Pharmaceuticals).

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1986, but has been relatively little employed (Russo 2002). Reasons include expense, delayed onset of effects in the range of 90-120 minutes, lack of practical titration of dosage, and a pronounced tendency toward dysphoria or other mental complaints from being "too high." In part, this may relate to hepatic first-pass conversion of THC to 11-OH-THC, which may possess a higher degree of psychoactivity according to some authorities. Interestingly, the presence of CBD, which is present in natural cannabis, but obviously absent in Marinol®, impedes this hepatic conversion by inhibition of cytochrome P450 3A11 (Browne and Weissman 1981).

Although smoking of cannabis was an acknowledged delivery system in the past, with cigarettes from the Grimault et Cie Company among others, and endorsement by such experts as Walter E. Dixon in England (Dixon 1899, 1921) and Walther Straub in Germany (Straub

1931), it is highly unlikely that regulatory agencies such as the Food and Drug Administration (FDA) would ever approve a drug delivery system that produces bronchial irritation and contains pyrolytic end-products that are potentially carcinogenic (Tashkin et al. 2002). Vaporization technology presents a viable option, preserving as it does the rapid bronchial absorption of cannabis components, and retaining the ability to titrate dosage rapidly. It is in initial stages of investigation (Gieringer 1996; Gieringer 1996; Gieringer 2001; Russo and Stortz 2003). This approach will require both elucidation of the pharmacokinetics of the vaporization technique, and approval of the hardware as a medical device. As will be discussed, GWP has developed an inhaled device (patent application GB0126150.2) that employs a metallic or ceramic surface coated with CBME that is heated by electrical current. The process is triggered by inhalation, employing the Advanced Dispensing System (ADS) (*vide infra*) providing the advantages of smoked cannabis (rapid onset, ready dosage titratability), but without hazards posed by smoke particles or inhalation of solvents.

Inhaled, non-smoked delivery of isolated THC has been previously investigated (Tashkin et al. 1977), but curiously, the isolated molecule is quite irritating to the bronchioles and induces a cough reflex despite its notable bronchodilatory benefits (Williams, Hartley, and Graham 1976). Biophysical parameters for this method of delivery are exacting, and have been recently reviewed (Whittle, Guy, and Robson 2001). Particles of diameter greater than 10 μ fail to reach the bronchioles. Those below 1 μ are mostly re-expired. It is only those particles in the 1-2 μ range that stand the best chance to be absorbed from the alveoli. Inasmuch as THC is an extremely viscous molecule that sticks to any vessel, dispersion in a solvent such as alcohol or propylene glycol is most often necessary, and introduces its own adverse effect issues in pulmonary application. This search for modern alternatives to smoked cannabis continues, however, through the use of a metered dose inhaler (Wilson et al. 2002) for THC. Although some seemingly represent that THC represents the sum total of important pharmacological effects of cannabis (Wachtel et al. 2002), others counter (McPartland and Russo 2001; Russo and McPartland 2003) in contrast, that the presence of other phytocannabinoid and terpenoid component such as myrcene, with its analgesic and anti-inflammatory effects (Rao, Menezes, and Viana 1990; Lorenzetti et al. 1991), or α-pinene, which is also a bronchodilator (Falk et al. 1990), or apigenin, wich is a non-sedating flavonoid in cannabis (Viola et al. 1995), contribute demonstrably to its clinical attrib-

utes. This debate will continue, engendering as it does the basic conflict between single-component "modern" pharmacology, and old-fashioned but resurgent notions of phytotherapeutic synergy.

Suppository forms of cannabis have been documented as far back as Ancient Egypt (Mannische 1989; Russo 2002), and the Victorian era (Farlow 1889). Modern research effort has also revived the concept, most often with Δ^9-THC-hemisuccinate (Broom et al. 2001; Elsohly et al. 1991). This method lacks convenience, is less subject to allow titration of dosage, and may be cosmetically unacceptable, especially in particular American consumers.

Transdermal delivery of cannabinoids is an attractive possibility as consumers have found "patches" to be a convenient method of drug delivery via this parenteral, long-acting method. Problems with this method have been previously outlined (Whittle, Guy, and Robson 2001). In essence, they include the lipophilic nature of cannabis components, the need for carrier molecules or other facilitators of transdermal absorption, and results to date that approximate only 10% of necessary serum levels (Challapalli and Stinchcomb 2002). Finally, the gradient of transport of cannabinoids through the skin is such that a used patch would still retain 90% or more of initial dosage, and would thereby represent a theoretical diversion risk upon disposal.

GW Pharmaceuticals primary efforts to date have focused on an approach employing a sub-lingual or oro-mucosal spray of CBME in ethanol and propylene glycol solution. The oro-mucosal preparation employs a pump action aerosol spray (Robson and Guy 2003; Whittle and Guy 2003) (Figure 6). This dispersion of materials allows reasonably rapid absorption (45 minutes), preserving the ability to titrate dosage, avoiding excessive swallowing of material, and producing an area under the curve that is comparable to that for smoked or intravenous administration of THC (Whittle and Guy 2003). Experiments in the UK with a simple unadorned device have demonstrated no major compliance problems, nor diversion of CBME to the black market. There are no plans to introduce pharmaceutical products with CBME in the UK, Western European or British Commonwealth nations with added security devices. However, it is anticipated that such security would be a necessary prerequisite in the USA for Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA) approval (Figure 7). Thus, an additional Advanced Delivery System (ADS) has been developed (Figure 8). The ADS is a hand-held computerized encrypted device which may (Robson and Guy 2003; Whittle and Guy 2003):

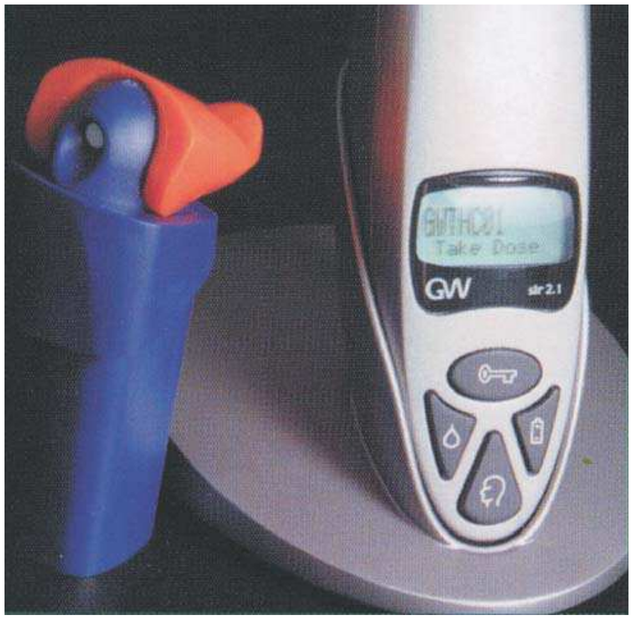
1. remind patients of times dosing is due
2. record daily patterns and fluctuations in doses employed
3. allow remote computer monitoring of dosage employed by researchers or clinicians
4. render the device secure, tamper-proof, and patient-specific through individual codes
5. allow delivery of a variety of dosage forms (e.g., CBME with THC-CBD 1:1 ratio for daily usage, with high-THC preparation for sudden bouts of pain)
6. be suitable for usage with controlled drugs such as methadone or diamorphine (heroin).

CLINICAL STUDY DESIGN

As will be seen subsequently, initial Phase I studies of CBME examined pharmacokinetics and adverse effects of the materials in normal

FIGURE 6. Pump Action Sublingual Spray as utilized in the United Kingdom (photograph courtesy of GW Pharmaceuticals).

FIGURE 7. Sublingual spray as part of Advanced Delivery System (photograph courtesy of GW Pharmaceuticals).



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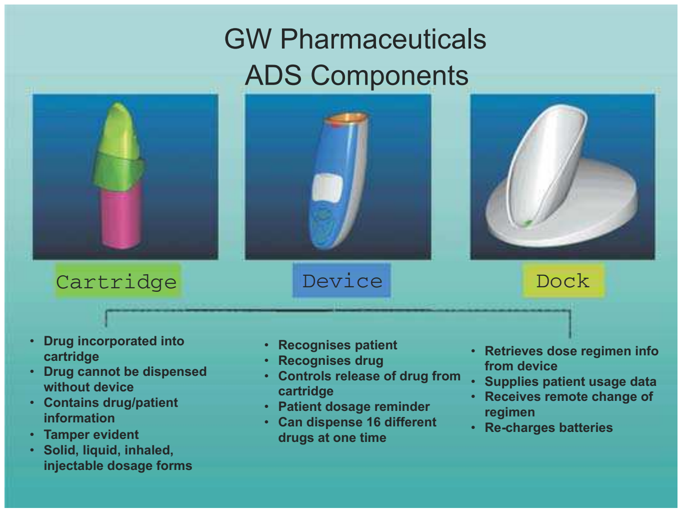
volunteers with monitoring of dose-response parameters, as well as pulse, blood pressure and subjective and objective assessments of intoxication. Although criticized, the current "gold standard" in pharmaceutical assessment is the double-blind randomized placebo-controlled clinical trial (RCT). An accepted variation in this approach that is worthwhile in contexts in which true blinding is difficult to achieve (as with cannabis) or in assessment of unpredictable diseases (such as multiple sclerosis) is presented by the N-of-1 trial design, achieved through a series of randomized, placebo controlled studies in which each subject serves as their own control (Guyatt et al. 1990). In fact, this approach to cannabis clinical trials was specifically endorsed by the American Institute of Medicine (Joy, Watson, and Benson 1999).

In assessing target conditions for initial studies, GWP relied on a survey of clinical cannabis patients and their conditions. In 1998, some 3516 self-selected patients who contacted the company were sent survey forms, of which 2458 were completed (70% response rate) (Robson and Guy 2003). Of 787 current or past cannabis users, the greatest rep-

FIGURE 8. Diagram of Advanced Delivery System (ADS) (courtesy of GW Pharmaceuticals).



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resentation was among patients with MS or various arthritic conditions. This contrasts with the situation in the USA, where HIV/AIDS is more highly represented, but where chronic pain remains a prime concern (Corral 2001; Gieringer 2001).

Another priority in selection of patients for clinical investigation involved a decision to study those with intractable conditions that had failed to be symptomatically controlled by available conventional pharmaceuticals. This was based on a philosophical decision to demonstrate that CBME would not merely be equal in efficacy to standard drugs, but rather, offer tangible advantages in difficult clinical contexts. A decision was also made to add CBME to patients' existing pharmaceutical regimens to provide a baseline comparison.

For MS patients, entry criteria included the presence of one or more poorly controlled symptom despite best available treatment: pain, spasm, spasticity, tremor or urinary difficulty, whether frequency, urgency, nocturia or incontinence (Robson and Guy 2003; Whittle and Guy 2003). Patient exclusions were similar to those employed in previous studies of cannabis or Marinol®: history of serious drug or alcohol abuse, schizophrenia, uncontrolled cardiovascular conditions including hypertension, impaired hepatic or renal function, and epilepsy. All na-

tional norms for clinical research and Guidelines for Good Clinical Practice (GCP) were followed.

Noting past historical data on individual idiosyncrasies of dosing and responses to cannabis by patients, a requirement was pursued to deliver initial THC:CBD 1:1 CBME dosages in open-label fashion with close monitoring, in an attempt to establish initial individual dose guidelines. This was then followed by randomized double-blind crossover comparisons of that preparation versus placebo and high-THC and high-CBD CBMEs. Subsequent monitoring employed an array of subjective measures (via visual analogue scales, or VAS) and objective measures on examination and laboratory study. Patients who demonstrated benefits in initial studies were given the option of entering long-term safety studies, and a majority of patient-subjects chose to do so (Robson and Guy 2003). The results of these trials form the basis for the remainder of this publication.

THC AND CBD: SUMMARY OF CURRENT KNOWLEDGE

Although this author has emphasized the biochemical and physiological contribution importance of other cannabis components (minor cannabinoids, terpenoids and flavonoids) to the medical therapeutic benefits of cannabis (McPartland and Russo 2001), it is clear from the data that exist to date that two entities provide the greatest effects: Δ^9-tetrahydrocannabinol and cannabidiol. A complete analysis of current knowledge is beyond our scope, but it is appropriate to briefly summarize current knowledge of their contributions (Table 1).

Receptor Effects

THC is a partial agonist at both CB_1 and CB_2 receptors (Pertwee 1998; Showalter et al. 1996). In contrast, CBD has little activity, and perhaps slight antagonistic activity at CB_1, while greater activity at CB_2 (Showalter et al. 1996). Of great importance, it has recently been demonstrated that cannabidiol stimulates vanilloid receptors (VR_1) with similar efficacy to capsaicin, and inhibits uptake of the endocannabinoid anandamide (AEA), and weakly inhibits its hydrolysis (Bisogno et al. 2001). These new findings have important implications in elucidating the pain-relieving and anti-inflammatory effects of CBD. In a

TABLE 1. Therapeutic/Adverse Effects of THC and CBD

Effect	THC	CBD	Reference
Receptor/Non-Receptor Effects			
CB_1 (CNS receptors)	++	±	(Pertwee 1998)
CB_2 (Peripheral receptors)	+	++	(Showalter et al. 1996)
Vanilloid Receptors	−	+	(Bisogno et al. 2001)
Anti-inflammatory	+	+	(Hampson et al. 1998)
Immunomodulatory	+	++	(Malfait et al. 2000; Cabral 2001)
CNS Effects			
Anticonvulsant	+	++	(Wallace, Martin, and DeLorenzo 2002; Carlini and Cunha 1981)
Muscle Relaxant	+	++	(Petro 1980)
Antinociceptive	++	+	(Pertwee 2001)
Catalepsy	++	++	(O'Shaughnessy 1838-1840)
Psychotropic	++	−	(Russo 2001)
Anxiolytic		+	(Zuardi and Guimaraes 1997)
Antipsychotic	−	++	(Zuardi and Guimaraes 1997)
Neuroprotective antioxidant activity	+	++	(Hampson et al. 1998)
Antiemetic	++	−	(Chang et al. 1979)/(Guy et al. 2002)
Sedation (reduced spontaneous activity)	+	+	(Zuardi and Guimaraes 1997)
Agitation (Alzheimer disease)	+		(Volicer et al. 1997)
Tic reduction	+		(Müller-Vahl et al. 1999)
Withdrawal effects (reduction)	+		(Cichewicz and Welch 2002; Reynolds 1890)
Migraine	+		(Russo 2001; Russo 1998)
Bipolar disease	+		(Grinspoon and Bakalar 1998)
Cardiovascular Effects			
Bradycardia	−	+	(Weil, Zinberg, and Nelsen 1968)
Tachycardia	+	−	ditto
Hypertension	+	−	ditto
Hypotension	−	+	(Adams et al. 1977)
Appetite/Gastrointestinal			
Appetite	+	−	(da Orta 1913)
Motility (slowed)	+		(Pertwee 2001)
Neonatal feeding (endocannabinoid)	+		(Fride 2002)
Anti-Carcinogenesis			
Melanoma (apoptosis, angiogenesis)	+		(Casanova et al. 2003)
Breast (prolactin receptor)	+		(De Petrocellis et al. 1998)
Glioma (apoptosis)	+	+	(Sanchez et al. 1998; Vaccani, Massi, and Parolaro 2003)
Leukemia (apoptosis)	+		(McKallip et al. 2002)
Pulmonary (blocks carcinogenesis enzymatically)	+		(Roth et al. 2001)
Pulmonary			
Bronchodilation	+		(Williams, Hartley, and Graham 1976; Tashkin et al. 1977)
Ophthalmological			
Intra-ocular pressure (reduced)	++	+	(Merritt et al. 1980; Jarvinen, Pate, and Laine 2002)
Night vision (improved)	+*		(Russo et al. 2003; West 1991)

Adapted and expanded from (Whittle, Guy, and Robson 2001; Whittle and Guy 2003).
* New indication. See final article in this publication.

manner of interpretation, CBD may be considered the first clinical agent that modulates endocannabinoid function.

Anti-Inflammatory and Immunomodulatory Effects

The benefits of cannabis and cannabinoids on inflammation have been extensively documented. The following are suggested as reviews (Hampson et al. 1998; Pertwee 2001; Burstein 1992; Russo 2001). Both THC and CBD have important roles in these observations. Of increasing interest is the recent demonstration that CBD possesses both anti-inflammatory and immunomodulatory benefits in an animal model of rheumatoid arthritis (Malfait et al. 2000). Although there has been great concern expressed as to immunological damage by cannabis, such effects are usually demonstrable in laboratory assays at levels 50-100 times the psychoactive dose (Cabral 2001). Deleterious clinical effects of cannabis in HIV (Abrams et al. 2002), and chronic medical usage (Russo et al. 2002) have not been demonstrated.

Central Nervous System Effects

Of prime importance in cannabinoid therapeutics is pain control or antinociception (Pertwee 2001; Russo 2001). One of the primary functions of the endogenous cannabinoid system is modulation of pain control, in parallel with the endogenous opioid and vanilloid systems. THC is the main contributor of cannabis to control of pain, via its actions on CB_1, which occur in key areas of the spinal cord, and brainstem. A purported "comprehensive" review of the analgesic effects of cannabinoids concluded that they have little demonstrated benefit (Campbell et al. 2001), but this pronouncement produced strong refutation (Russo 2001) and more considered subsequent support (Baker et al. 2003) in some quarters. Countless testimonials attest to the unique benefits of cannabis in difficult cases of neuropathic pain (Grinspoon and Bakalar 1997), and other unusual and intractable conditions, such as familial Mediterranean fever (Holdcroft et al. 1997).

The cataleptic effects of high doses of THC were noted by O'Shaughnessy in 1839 (O'Shaughnessy 1838-1840), and this effect remains part of the tetrad of behavioral effects sought in laboratory animals as a sign of cannabinoid activity.

Cannabis was noted to have anticonvulsant effects in the 19th century. Primary focus of therapeutic benefit on seizures of partial onset has focused on CBD (Carlini and Cunha 1981), while it was generally

believed that THC was proconvulsant. Epileptic patients have generally claimed otherwise (Corral 2001), and it was recently demonstrated that endocannabinoids modulate seizure thresholds, and that THC exerts an anticonvulsant effect, as well (Wallace, Martin, and DeLorenzo 2002).

Migraine is a neurochemical and vascular disorder of exceeding complexity, whose treatment remains extremely problematical. The multi-modality effects of cannabis seem to support its historical role in both symptomatic and prophylactic treatment (Russo 1998; Russo 2001). While THC has received the bulk of the attention in therapeutic application, this author's experience with Marinol® treatment would seem to support that the benefits on chronic migraine treatment do not mirror the high efficacy of historical claims in the Victorian era. Current discoveries of the endocannabinoid modulation and vanilloid receptor effects of CBD discussed above (Bisogno et al. 2001) would seem to support that cannabidiol is a necessary component to successful prophylaxis in migraine.

Antidepressant and anti-anxiety effects of cannabis date to ancient India in the *Atharva Veda*, and the Scythians (Herodotus 1998). Certainly, an antidepressant effect of cannabis has been observed in chronic disease (Herodotus 1998; Russo et al. 2002; Regelson et al. 1976). In general, THC is considered psychotropic, while CBD generally is not (reviewed in Russo 2001). Rather, cannabidiol is noteworthy for its anxiolytic, sedative and antipsychotic effects (Zuardi and Guimaraes 1997). Interestingly, THC (as Marinol®) was recently observed to produce weight gain and reduce agitation in demented Alzheimer disease patients (Volicer et al. 1997). Unfortunately, CBD was not examined, but very likely would have contributed to the clinical benefits. Anecdotal reports support benefit of THC in mood-stabilization in bipolar disease (Grinspoon and Bakalar 1998).

The antispasmodic effects of cannabis were observed in such diseases as tetanus in the 19th century, producing cures of fatal diseases, and palliation of chronic disorders (O'Shaughnessy 1838-1840). Muscle relaxant properties of cannabis in multiple sclerosis were noted more recently (Petro 1980; Grinspoon and Bakalar 1997), and have recently been reviewed in detail (Baker et al. 2003; Consroe 1998; Petro 2002). These will form the focus of many of the study results subsequently discussed in this publication. As if the muscle relaxant and anti-spasmodic benefits of cannabis were insufficient, it has recently been demonstrated that cannabinoid agonists positively influence the immunological parameters of demyelinating diseases such as experimentally allergic encephalomyelitis (Baker et al. 2000). In the past year,

a small clinical trial of THC and a cannabis extract was performed with 16 subjects. Neither was observed to reduce spasticity, and adverse events were reported in the extract group (Killestein et al. 2002). Numerous criticisms were subsequently voiced in this regard (Russo 2003). Among these were that the plant extract was poorly categorized; in fact, it contained a fixed ratio of THC to CBD with maximum doses of 5 mg of THC and 2 mg of CBD per day. The study additionally employed oral administration with no real dose titration. An additional study in Switzerland with more patients (57) and doses of up to 15 mg THC with 6 mg CBD divided tid has provided better results with reduction in spasms to the $p < 0.05$ level and no significant side effects vs. placebo (Vaney et al. 2002). A study of an even larger cohort of MS patients in the UK is pending publication.

Kirsten Müller-Vahl has pioneered the use of cannabis and THC in Tourette syndrome, demonstrating a marked reduction in tic behavior and obsessive-compulsive preoccupation (Muller-Vahl et al. 2003; Müller-Vahl et al. 1999).

The antiemetic effect of THC in morning sickness was noted as early as the 19th century (Wright 1862), and was further elucidated in the last two decades (Chang et al. 1979). A tremendous body of knowledge in this context that has been historically ignored was recently published in this journal (Musty and Rossi 2001). This pertained to state-sponsored studies in the USA in cancer chemotherapy. Pooling available data in some 768 patients, oral THC provided 76-88% relief of nausea and vomiting, while smoked cannabis figures supported 70-100% relief in the various surveys. Also worthy of inclusion here, an Israeli study of 8 children receiving highly emetogenic chemotherapy for hematological malignancies with oral Δ^8-THC (a trace and more stable component of cannabis) was 100% effective in allaying vomiting in 480 dose applications! Surprisingly, slight euphoria was noted in only one subject, causing the authors to surmise that the appreciation of the cannabis "high" is a developmental phenomenon. Shockingly, this study has never been followed by more similar investigations.

Surprisingly as well, it has just been demonstrated that CBD also has anti-emetic benefits in motion sickness in rodents (Guy et al. 2002), an indication that has wide implications, including space flight.

Although THC and cannabis are often attacked as productive of addiction, it is well documented from the 19th century that prominent physicians claimed benefit of Indian hemp in treatment of alcohol, morphine and cocaine dependencies (Reynolds 1890). As is becoming a recurrent

theme, the claims of the Victorian era are resonating with modern scientists who subsequently prove their biochemical and physiological basis. This benefit has been strikingly demonstrated in the laboratory, through "opiate-sparing" by THC (Cichewicz et al. 1999), and more recently, the effect of THC to mitigate opiate-withdrawal symptoms, and block the formation of dependency (Cichewicz and Welch 2002).

One of the most exciting and pressing areas of neurological investigation surrounds the emerging concept of neuroprotection. If one were able to prevent the progressive cell death of parkinsonism, amyotrophic lateral sclerosis, Alzheimer and Huntington diseases, the inevitable deterioration and ultimate demise that these disorders eventuate might well be mitigated or arrested. This is the promise that may accrue to THC and CBD from the research of Hampson et al. (1998) in their demonstration that these agents are capable of blocking NMDA receptors in glutamate toxicity.

Cardiovascular Effects

A pioneering study in 1968 documented transient tachycardia and hypertension induced by THC in experimental subjects (Weil, Zinberg, and Nelsen 1968). Overall however, a mild hypotensive effect of CBD is observed (Adams et al. 1977). Recently, concerns have been raised with respect to cannabis as an inciting influence in myocardial infarction (Mittleman et al. 2001), but no significant epidemiological basis is evident for such claims (Sidney et al. 1997).

Appetite/Gastrointestinal

The appetite stimulating power of cannabis and THC are among the most well known effects (or side effects). This phenomenon was first documented in the West by the physician and explorer, Garcia da Orta, in India in the 16th century (da Orta 1913), but repeatedly studied subsequently. It was this effect that led to an approved indication for THC (as Marinol®) in the USA in 1992. Recently, smoked cannabis and THC demonstrated benefits in appetite and weight gain in hospitalized AIDS subjects (Abrams et al. 2002).

THC slows gut motility (reviewed in Pertwee 2001), providing additional support to the known analgesic and anti-inflammatory benefits in such disorders as Crohn's disease, ulcerative colitis, and idiopathic bowel syndrome (spastic colon).

A much better understanding of the critical role of tonic endocannabinoid function in normal ontogeny has recently been elucidated when Ester Fride and colleagues investigated the role of anandamide in initiation of neonatal feeding, and inevitable demise with its blockade (Fride 2002). Therapeutic use in "failure-to-thrive" states and cystic fibrosis (Fride 2002) are obvious putative applications.

Anti-Carcinogenesis

Whereas, governmental pronouncements have long sought to indict marijuana and THC as contributors to the incidence of cancer, closer analysis has failed to demonstrate epidemiological support for significant danger, even with smoked cannabis (Ware and Tawfik 2001). Little publicity, in contrast, has accrued to an increasing number of studies that demonstrate anti-carcinogenesis by THC.

Legitimate concerns surround the use of smoked cannabis, and its contribution to pulmonary irritation, bronchitis symptoms, and possible neoplastic sequelae (Tashkin 2001). However, recent study indicates that THC and even cannabis smoke block the activity of a key enzyme in pulmonary carcinogenesis (Roth et al. 2001), perhaps explaining the observation that there are still no documented cases of lung cancer in cannabis-only smokers.

THC also has been demonstrated to promote apoptosis (programmed cell death) in malignant conditions including: leukemia (McKallip et al. 2002) via CB_2 stimulation, gliomas (Sanchez et al. 1998), and melanoma (Casanova et al. 2003), in which tumor angiogenesis is also inhibited. Additionally, two types of breast tumor cell lines were inhibited by THC (De Petrocellis et al. 1998), apparently via prolactin receptor effects. This is obviously a fertile area for further research.

Pulmonary

As noted above, the primary medical concerns about cannabis revolve around its pulmonary sequelae. It requires emphasis that these may be totally avoided through alternative delivery techniques. That notwithstanding, it seems that emphysematous deterioration, even in cannabis smokers, is a lower risk than previously surmised (Tashkin et al. 1997). Actual therapeutic application of THC in asthma, as previously attempted (Tashkin et al. 1977; Williams, Hartley, and Graham 1976), may soon become a reality with improved vaporizers or CBME applications.

Ophthalmological

The ability of cannabis and THC to lower intra-ocular pressure in glaucoma was serendipitously discovered in the late 1970s by a variety of patients and researchers (Randall and O'Leary 1998; Merritt et al. 1980). What is more compelling perhaps, in the long run, is the fact that there is more to glaucoma treatment than merely controlling pressure. Even effective management with conventional pharmacology fails to avert visual loss over time. Rather, an emerging concept supports that prospect that glaucoma represents a progressive vascular retinopathy that requires a neuroprotectant to preserve vision (Jarvinen, Pate, and Laine 2002). This is an area where cannabis and cannabinoids shine.

As will be discussed in the final entry in this publication, cannabis and cannabinoids also seem to have a role in improving night vision and in treatment of other degenerative eye conditions (Russo et al. 2003).

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GW Pharmaceuticals List of Abbreviations and Definitions of Terms

Abbreviation/Term	*Definition/Explanation*
°C	Degrees Celsius
AE	Adverse Event
$AUC_{0-\infty}$	The area under the plasma concentration versus time curve from zero to t calculated as AUC_{0-t} plus the extrapolated amount from time t to infinity
AUC_{0-t}	The area under the plasma concentration versus time curve, from time zero to 't' (where t = the final time of positive detection) as calculated by the linear trapezoidal method
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BMI	Body Mass Index; Weight (kg)/Height (m^2)
BP	Blood Pressure (systolic and diastolic)
BS-11	Box Scale 11
CBD	Cannabidiol
CBME	Cannabis Based Medicine Extract
CI	Confidence Interval

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Abbreviation/Term	*Definition/Explanation*
C_{max}	Maximum measured plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CV%	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
Eth	Ethanol
GGT	Gamma Glutamyl Transferase
GCP	Good Clinical Practice
GW	GW Pharma Ltd/GW Pharmaceuticals Ltd
Hb	Haemoglobin
ICH	International Conference of Harmonisation
K_{el}	The Elimination Rate Constant
LLOQ	Lower Limit of Quantification
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
PG	Propylene Glycol
pg	Picogram
PK	Pharmacokinetic
ppmt	Peppermint
PR	PR segment in the tracing on the electrocardiogram
QT	QT segment in the tracing on the electrocardiogram
QT_c	QT segment in the tracing on the electrocardiogram corrected for breathing
QRS	QRS segment in the tracing on the electrocardiogram
RCC	Red Cell Count

Abbreviation/Term	*Definition/Explanation*
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
THC	Δ^9-Tetrahydrocannabinol
T_{max}	Time to the Maximum Measured Plasma Concentration
$t_{1/2}$	Half Life
WCC	White Cell Count

A Single Centre, Placebo-Controlled, Four Period, Crossover, Tolerability Study Assessing, Pharmacodynamic Effects, Pharmacokinetic Characteristics and Cognitive Profiles of a Single Dose of Three Formulations of Cannabis Based Medicine Extracts (CBMEs) (GWPD9901), Plus a Two Period Tolerability Study Comparing Pharmacodynamic Effects and Pharmacokinetic Characteristics of a Single Dose of a Cannabis Based Medicine Extract Given via Two Administration Routes (GWPD9901 EXT)

G. W. Guy
M. E. Flint

G. W. Guy and M. E. Flint are affiliated with GW Pharmaceuticals plc, Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, UK.

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SUMMARY. This study was the first study of GW's CBME in man. It was performed in six healthy subjects, employing test treatments consisting of CBD:THC sublingual drops (GW-1011-01): 5 mg Δ^9-tetrahydrocannabinol (THC) + 5 mg cannabidiol (CBD) per ml of glycerol:ethanol (Eth):propylene glycol (PG) (4:4:2), with peppermint flavouring, High CBD sublingual drops (GW-3009-01): 5 mg CBD per ml of glycerol: Eth:PG (4:4:2), with peppermint flavouring, High THC sublingual drops (GW-2009-01): 5 mg THC per ml of glycerol:Eth:PG (4:4:2), with peppermint flavouring, placebo sublingual drops (GW-4003-01): glycerol: Eth:PG (4:4:2), with peppermint flavouring, aerosol (GW-1009-01): 5 mg CBD + 5 mg THC per ml formulated in propellant:Eth (80:20), and nebuliser (GW-1012-01): 10 mg CBD + 10 mg THC per ml of cremophor (Crem) (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H_2O (7.4), and placebo nebuliser (administered to subjects 005 and 006 instead of the active nebuliser test treatment): Crem (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H_2O (7.4).

Periods 1, 5 and 6 were open label, Periods 2 to 4 double blind. The study was a partially randomised crossover using single doses of THC and/or CBD or placebo. The study drug was administered as sublingual drops according to a pre-determined randomisation scheme in Periods 1 to 4. In Period 5, CBD:THC was administered as a sublingual aerosol and in Period 6 CBD:THC was administered as an inhalation via a nebuliser. There was a six-day washout between each dose.

Primary objectives of the study were to make a preliminary evaluation of the tolerability of cannabis based medicine extracts at single dose in comparison to placebo in order to provide guidance for dosage in future studies; GWPD9901 EXT: was designed to compare the effect of method of administration (sublingually via an aerosol) or the route (inhalation) on the cannabis based medicine extract containing THC and CBD in a ratio of 1:1 in terms of subjective assessment of well-being, *in vivo* pharmacokinetic characteristics over 12 h, the adverse event (AE) profile and measurement of vital signs and conjunctival reddening over 12 h.

Secondary objectives were to compare the effects of the four preparations in terms of cognitive assessment, subjective assessment of well-being *in vivo* pharmacokinetic characteristics over 12 h, the AE profile and measurement of vital signs and conjunctival reddening over 12 h.

The methodology was a six single dose, partially randomised, six-way cross-over study. In Period 1, all subjects received CBD:THC drops. In Periods 2-4, High THC drops, High CBD drops and placebo drops were administered, double blind and fully randomised. In Period 5, all subjects received the aerosol test treatment and in Period 6, all subjects received the nebuliser test treatment.

Each subject received five single doses of a maximum of 20 mg CBD, 20 mg CBD + 20 mg THC and 20 mg THC on five separate occasions

and a placebo dose on one occasion. The duration of the study was six weeks.

Following administration of CBD:THC (Sativex) sublingual drops, mean concentrations of CBD, THC and 11-hydroxy-THC were above the Lower Limit of Quantification (LLOQ) by 45 min post-dose. Plasma concentrations of THC were at least double those of CBD before both decreased below the LLOQ by 360 min and 480 min post-dose, respectively. When High CBD sublingual drops were administered, plasma levels of CBD were generally similar to those measured after CBD:THC sublingual drops. High THC resulted in marginally earlier detection of mean concentrations of both THC and 11-hydroxy-THC and a slightly earlier decline than for CBD:THC sublingual plasma concentrations. Following administration of CBD:THC via the pressurised aerosol, mean quantifiable levels of CBD and THC were detected marginally earlier than for the CBD:THC sublingual drops and declined below the LLOQ marginally later. Plasma concentrations of THC, 11-hydroxy-THC and CBD following administration via the aerosol were lower than after administration of the sublingual drops. Following administration of CBD:THC via the nebuliser, mean plasma levels of both CBD and THC increased rapidly (within 5 min) to levels much higher than measured following administration of the sublingual drops and were maintained until around 120 min post-dose before declining rapidly. Levels of 11-hydroxy-THC were very low compared with those after sublingual dosing.

There were no statistically significant differences in the pharmacokinetics of THC or CBD between CBD:THC sublingual drops and High THC, High CBD or pressurised aerosol. With the exception of a single statistically significant difference in $AUC_{0-\infty}$ for 11-hydroxy-THC following administration of the High THC compared with CBD:THC sublingual drops there were no significant differences in the PK of 11-hydroxy-THC either.

Dosing with the inhaled nebuliser produced marked differences in the pharmacokinetics of CBD and THC compared with CBD:THC sublingual dosing. Peak concentration was greater and much earlier although only C_{max} of CBD and T_{max} of THC were statistically significantly different. Peak concentration and AUCs of 11-hydroxy-THC were statistically significantly less, reflecting reduced early metabolism of THC by this route.

No consistent statistically significant differences were noted between the pharmacokinetic parameters of High CBD, High THC and the aerosol when compared to the CBD:THC sublingual drops. However, the nebuliser resulted in a rapid absorption of CBD and THC and higher peak plasma levels but a reduction in the metabolism of THC to 11-hydroxy-THC.

Subjects experienced a reduction in wakefulness, feeling of well-being, mood, production of saliva and increased hunger and unpleasant effect following administration of each test treatment and placebo. The maximum mean changes in wakefulness, feeling of well-being, mood and production of saliva were reported 3 h post-dose following administration of CBD:THC sublingual drops. Similar trends were also reported following administration of placebo and therefore it is suggested that the effects reported may not be entirely due to active test treatments. The greatest mean incidence of unpleasant effects was reported earlier than for any other effect and following administration of the nebuliser test treatment.

The sublingual test treatments were best liked and the nebuliser test treatment was least liked. All of the subjects (100%) reported coughing and three subjects (50%) reported a sore throat following dosing with the nebuliser.

The sublingual test treatments were well tolerated by all subjects. All six subjects experienced at least two AEs during the study, but there were no deaths, serious adverse events (SAEs) or other significant AEs. The commonest AEs were tachycardia, conjunctival hyperaemia and abnormal dreams.

The small variations in individual subject laboratory parameters and urinalyses and in the mean laboratory parameters did not suggest any patterns or trends. The mean values of all the vital signs showed no patterns or trends either and no differences from placebo. ECGs at both screening and post-study were normal for all subjects.

In conclusion, each sublingual test treatment was well tolerated by all subjects. The inhaled test treatment was not well tolerated and resulted in adverse effects.

KEYWORDS. Cannabinoids, cannabis, THC, cannabidiol, medical marijuana, pharmacokinetics, pharmacodynamics, multiple sclerosis, botanical extracts, alternative delivery systems, harm reduction

INTRODUCTION

Cannabis plants (*Cannabis sativa*) contain approximately 60 different cannabinoids (British Medical Association 1997) and in the UK, oral tinctures of cannabis were prescribed until cannabis was made a

Schedule 1 controlled substance in the Misuse of Drugs Act in 1971. The prevalence of recreational cannabis use increased markedly in the UK after 1960, reaching a peak in the late 1970s. This resulted in a large number of individuals with a range of intractable medical disorders being exposed to the drug, and many of these discovered that cannabis could apparently relieve symptoms not alleviated by standard treatments. This was strikingly the case with certain neurological disorders, particularly multiple sclerosis (MS). The black market cannabis available to those patients is thought to have contained approximately equal amounts of the cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Baker, Gough, and Taylor 1983). The importance of CBD lies not only in its own inherent therapeutic profile but also in its ability to modulate some of the undesirable effects of THC through both pharmacokinetic and pharmacodynamic mechanisms (McPartland and Russo 2001). MS patients claimed beneficial effects from cannabis in many core symptoms, including pain, urinary disturbance, tremor, spasm and spasticity (British Medical Association 1997). The MS Society estimated in 1998 that up to 4% (3,400) of UK MS sufferers used cannabis medicinally (House of Lords 1998).

Cannabinoid clinical research has often focussed on synthetic analogues of THC, the principal psychoactive cannabinoid, given orally. This has not taken the possible therapeutic contribution of the other cannabinoid and non-cannabinoid plant components into account, or the slow and unpredictable absorption of cannabinoids via the gastrointestinal tract (Agurell et al. 1986). Under these conditions it has been difficult to titrate cannabinoids accurately to a therapeutic effect. Research involving plant-derived material has often reported only the THC content (Maykut 1985) of the preparations, making valid comparisons between studies difficult.

GW has developed cannabis based medicine extracts (CBMEs) derived from plant cultivars that produce high and reproducible yields of specified cannabinoids. CBMEs contain a defined amount of the specified cannabinoid(s), plus the minor cannabinoids and also terpenes and flavonoids. The specified cannabinoids constitute at least 90% of the total cannabinoid content of the extracts. The minor cannabinoids and other constituents add to the overall therapeutic profile of the CBMEs and may play a role in stabilising the extract (Whittle, Guy, and Robson 2001). Early clinical studies indicated that sublingual dosing with CBME was feasible, well tolerated and convenient for titration. The concept of self-titration was readily understood by patients and worked

well in practice. Dosing patterns tended to resemble those seen in the patient controlled analgesia technique used in post-operative pain control; with small doses administered as and when patients require them, up to a maximal rate and daily limit (GW Pharmaceuticals 2002). The Phase 2 experience has supported some of the wide-range of effects reported anecdotally for cannabis. It has also shown that for most patients the therapeutic benefits of CBMEs could be obtained at doses below those that cause marked intoxication (the 'high'). This is consistent with experience in patients receiving opioids for pain relief, where therapeutic use rarely leads to misuse (Portenoy 1990; Porter and Jick 1980). Onset of intoxication may be an indicator of over-titration. However the range of daily dose required is subject to a high inter-individual variability.

The CBME GW-1000-02 is administered as an oromucosal spray, and contains an equal proportion of THC and CBD, similar to the cannabinoid profile of the cannabis thought to be most commonly available on the European black market (Baker, Gough, and Taylor 1983). The CBME GW-2000-02 is administered as an oromucosal spray, and contains over 90% THC. In this study, the CBME was administered sublingually as drops (GW-1011-01, GW-3009-01, GW-2009-01 and GW-4003-01), a pressurised aerosol (GW-1009-01) and as an inhalation via a nebuliser (GW-1012-01). Each formulation contained either equal amounts of CBD and THC, CBD alone or THC alone.

GWPD9901 was a Phase I clinical study designed to investigate the tolerability, cognitive effects, pharmacokinetic (PK) and pharmacodynamic (PD) effects of CBD and THC when co-administered and administered alone. It was also designed to assess safety and tolerability of the test treatments. It was the first exposure in man of GW's CBME formulations.

STUDY OBJECTIVES

Primary objectives of GWPD9901 were to make a preliminary evaluation of the tolerability of cannabis based medicine extracts (CBMEs) at single dose in comparison to placebo in order to provide guidance for dosage in future studies; while in GWPD9901 EXT: they were to compare the effect of method of administration (sublingually via an aerosol) or the route (inhalation) on the cannabis based medicine extract containing THC and CBD in a ratio of 1:1 in terms of subjective assessment of well-being, *in vivo* pharmacokinetic characteristics over 12 h, the ad-

verse event (AE) profile and measurement of vital signs and conjunctival reddening over 12 h. Secondary objectives of GWPD9901 were to compare the effects of the four preparations in terms of cognitive assessment, subjective assessment of well-being *in vivo* pharmacokinetic characteristics over 12 h, the AE profile and measurement of vital signs and conjunctival reddening over 12 h.

INVESTIGATIONAL PLAN

Periods 1, 5 and 6 were open label, Periods 2 to 4 double blind. The study was a partially randomised crossover using single doses of THC and/or CBD or placebo. In Period 1, each subject received CBD:THC as a series of sublingual drops. In Periods 2 to 4, the High CBD, High THC and placebo were administered as a series of sublingual drops according to a pre-determined randomisation scheme. In Period 5, the aerosol test treatment was administered sublingually via a pressurised aerosol and in Period 6 the test treatment was administered as an inhaled dose via a nebuliser. There was a minimum washout period of six-days between each dose.

Blood samples were taken for plasma concentration analysis and blood pressure (BP) and pulse, cognitive testing (Periods 1 to 4 only) and PD effects were measured and recorded at pre-determined times during each study period.

Six healthy subjects (three male and three female) who complied with all the inclusion and exclusion criteria were required to complete the study in its entirety.

The CBD:THC sublingual drops were administered in Period 1 as the combination of CBD and THC was thought to be safest and allow assessment of the tolerability of the other test treatments. High CBD, High THC and placebo sublingual drops were then fully randomised to prevent period effect and this part of the study was also double blind to ensure no bias was introduced when recording AEs and other parameters.

The pressurised aerosol and inhaled nebuliser routes of administration were chosen to assess different methods of dose administration. These doses were not blinded or randomised due to the contrasting method of administration.

Subjects were admitted to the clinical unit the evening before dosing (Day−1) to allow dietary control and eligibility assessments to be made. Dose administration was in the morning of Day 1 of each period to al-

low for measurements/assessments to be carried out up to 12 h post-dose with minimal disruption to the subjects sleep. A crossover design was chosen to enable both inter- and intra-subject comparisons of the data collated. A six-day washout period was chosen as it was estimated that plasma concentrations of cannabinoids would be below the Lower Limit of Quantification (LLOQ) before administration of the next dose and to facilitate scheduling within the clinical unit.

This was a proof of concept study and therefore a small number of subjects (six) were required.

INCLUSION CRITERIA

For inclusion in the study, subjects were required to fulfil all of the following criteria:

1. Were aged 30-45 years.
2. Weighed between 50-90 kg inclusive and body mass index (BMI) no greater than 30 kg/m^2.
3. Were willing and able to undertake all study requirements including pre- and post-study medical screening.
4. Had given written informed consent.
5. Female: were surgically sterilised or were taking adequate contraceptive precautions.
6. Male: agreed to use barrier methods of contraception both during and for three months after completing the study.
7. Were cannabis experienced but had abstained for a minimum of 30 days prior to receiving the first dose.

EXCLUSION CRITERIA

Subjects were deemed not acceptable for participation in the study if any of the following criteria applied:

1. Had evidence of clinically significant cardiovascular, haematological, hepatic, gastro-intestinal, renal, pulmonary, neurological or psychiatric disease.
2. Had a history of schizophrenic-type illness.
3. Had a history of chronic alcohol or drug abuse or any history of social drug abuse other than experience with cannabis.

4. Had a resting systolic blood pressure (SBP) greater than 140 mmHg or diastolic blood pressure (DBP) greater than 90 mmHg.
5. Had a history of sensitivity to cannabis or multiple allergies or drug sensitivities.
6. Had a history of asthma.
7. Were currently taking any medication including self-medication.
8. Had taken a regular course of medication within the four weeks prior to first test treatment administration.
9. Had taken any medication within the fourteen days prior to first test treatment administration except for vitamins (which were required to be discontinued at screening), or the occasional use of paracetamol or, for females only, contraceptive preparations.
10. Had been hospitalised for any reason within the twelve weeks prior to first test treatment administration.
11. Had lost or donated greater than 400 ml of blood in the twelve weeks prior to first test treatment administration.
12. Had participated in a clinical trial in the 12 weeks prior to first test treatment administration.
13. Smoked more than five cigarettes a day.
14. Consumed more than 21 units of alcohol per week (male) or 14 units (female).
15. Had positive results for Hepatitis B or C, or Human Immunodeficiency Virus (HIV) 1 or 2 screening.
16. Had clinically significant biochemistry, haematology or urinalysis results at screening.
17. Were pregnant or lactating (females).
18. Refused to use the designated contraceptive precautions (male or female).
19. Failed to pass the Hospital Depression and Anxiety Scale (HADS) (reference to the Cognitive Assessment tests).
20. Were found to be colour blind (Ishihara colour blind screening).

STUDY RESTRICTIONS

Subjects were required to abstain from the following for the duration of the study:

i. All foods and beverages containing caffeine and alcohol for 48h pre-each dose until the end of each confinement period;

ii. Drinking more than 3 units (male) or 2 units (female) of alcohol per day during non-restricted days.
iii. Taking any drugs, including drugs of abuse, prescribed and/or over-the-counter medications for four weeks prior to first dose and for the duration of the study.

REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

The subjects were free to withdraw from the study without explanation at any time and without prejudice to future medical care. Subjects may have been withdrawn from the study at any time if it was considered to be in the best interest of the subject's safety.

TEST TREATMENTS ADMINISTERED

All subjects received a single dose of the allocated test treatment on Day 1 of each of the six periods. All subjects received five single doses (maximum of 20 mg CBD and/or THC per dose) of CBD and/or THC and one placebo dose. Preparations were as follows (Table 1).

Test treatments consisted of CBD:THC sublingual drops (GW-1011-01): 5 mg Δ^9-tetrahydrocannabinol (THC) + 5 mg cannabidiol (CBD) per ml of glycerol:ethanol (Eth):propylene glycol (PG) (4:4:2), with peppermint flavouring, High CBD sublingual drops (GW-3009-01): 5 mg CBD per ml of glycerol:Eth:PG (4:4:2), with peppermint flavouring, High THC sublingual drops (GW-2009-01): 5 mg THC per ml of glyc-

TABLE 1. Product Codes, Batch Numbers and Expiry Dates for Each Test Treatment

Treatment	*Batch No.*	*Product Code*	*Expiry Date*	*Total Dose*	*No. of Drops/Sprays/ Inhalations*
CBD:THC SL Drops	90903	GW-1011-01	Oct 31, 1999	20 mg CBD + 20 mg THC	8 (10 mins apart)
CBD SL Drops	90902	GW-3009-01	Oct 31, 1999	20 mg CBD	8 (10 mins apart)
THC SL Drops	90901	GW-2009-01	Oct 31, 1999	20 mg THC	8 (10 mins apart)
Aerosol	91001	GW-1009-01	Nov 21, 1999	20 mg CBD + 20 mg THC	8 (10 mins apart)
Nebuliser	91002	GW-1012-01	Oct 27, 1999	20 mg CBD + 20 mg THC	series of 50 breaths (5 mins apart)

SL = sublingual

erol:Eth:PG (4:4:2), with peppermint flavouring, placebo sublingual drops (GW-4003-01): glycerol:Eth:PG (4:4:2), with peppermint flavouring, aerosol (GW-1009-01): 5 mg CBD + 5 mg THC per ml formulated in propellant:Eth (80:20), and nebuliser (GW-1012-01): 10 mg CBD + 10 mg THC per ml of cremophor (Crem) (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H_2O (7.4), and placebo nebuliser (administered to subjects 005 and 006 instead of the active nebuliser test treatment): Crem (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H_2O (7.4).

Each test treatment container was identified with no less than study number, subject number, period number, unit number and expiry date. All subjects received CBD:THC sublingual drops in Period 1, the aerosol test treatment in Period 5 and the inhaled nebuliser test treatment in Period 6. High CBD, High THC and placebo sublingual drops were randomised in Periods 2 to 4 according to the randomisation scheme. The doses were chosen as they were considered to be the average dose of cannabinoids received by smoking a cannabis cigarette. Subjects were allowed to stop dosing at any time if effects were too unpleasant. The Principal Investigator was also permitted to stop dosing before the maximum of 20 mg CBD and/or 20 mg THC was achieved if it was considered that the PD effects were too great.

Subjects 005 and 006 received placebo via the nebuliser to determine if the adverse effects that subjects 001 to 004 had experienced were due to the method of administration or the active ingredient.

The test treatments were administered in the morning of each dosing day according to the randomisation scheme. Subjects were dosed in the morning to allow for measurements to be taken and procedures to be carried out to prevent the subjects being confined to the clinical unit overnight after dosing. A minimum of six-days washout between each dose was specified as it was considered that by that time, plasma cannabinoid concentrations would be below the LLOQ.

BLINDING

Periods 1, 5 and 6 were open label. Periods 2 to 4 were double blind. Unblinding envelopes were retained at the study centre and a duplicate set was retained at GW. All subjects completed the study without any serious adverse events (SAEs), therefore unblinding of any subject test treatment was not required. Upon completion of the in-life phase of the study, all unblinding envelopes were returned to GW intact.

Subjects were required to abstain from taking any medication in the 14 days, and/or taking a course of medication in the four weeks prior to the study commencing. Any medications taken by subjects during the study (screening to post-study examination) were recorded in the Case Report Form (CRF) and Investigator judgement as to the subjects' continued eligibility was made.

TREATMENT COMPLIANCE

Subjects were dosed by the Principal Investigator or suitably trained designee. For the sublingual drops and pressurised aerosol test treatments, subjects were instructed to allow each drop/spray to absorb under their tongue and not to swallow for as long as possible. For the nebuliser test treatment, subjects were instructed to breathe normally whilst inhaling through the nebuliser. The nebuliser was breath activated and subjects were instructed to inhale for 50 breaths over approximately 5 min, stop and repeat after 10 min. This process was required to be repeated until the maximum dose was reached or dosing was stopped. The actual time of administration of each drop/spray was recorded in the CRF and the dosing procedure was witnessed by a dose verifier. Due to a problem with the nebuliser, which did not give the required dose over 50 breaths, subjects were permitted to take more than 50 breaths per series.

PRE-STUDY SCREENING

Subjects were required to undergo a pre-study screen no more than 14 days prior to first dose administration to determine their eligibility to take part in the study. Only those subjects who were healthy and complied with all the study requirements were deemed eligible for participation.

Demographic Data

The subjects' date of birth, age, sex, race, height, weight, body mass index (BMI), previous cannabis experience, tobacco and alcohol consumption were recorded.

Concomitant Medications and Medical History

Subjects were asked to provide details of any drugs, vitamins or medications they had taken in the previous four weeks or were currently taking. If taking vitamins or paracetamol at screening, subjects were required to stop taking them at screening to be eligible for the study. Previous medical history details were also recorded.

Physical Examination

Subjects underwent a physical examination to determine if there are any abnormalities in any body systems. Blood pressure (systolic/diastolic) and pulse were measured after the subject had been seated for no less than 5 min. A 12-lead electrocardiogram (ECG) was taken for each subject and assessed using the usual parameters.

Microscopy was required to be carried out on any abnormal urine samples. A pregnancy test was carried out on all urine samples from female subjects. The samples provided (male and female) were also used to screen for drugs of abuse. A blood sample was taken in an EDTA blood tube for haematology. A blood sample was taken in a gel blood tube for clinical chemistry. A blood sample was taken in a gel blood tube to screen for the presence of Hepatitis B and/or C and/or HIV.

Subjects were required to complete the HADS test and the Ishihara Colour Blindness test.

PRE-DOSE PROCEDURES

The day before dosing for Period 1, subjects were required to attend the clinical unit in the afternoon to complete a baseline well-being questionnaire and cognitive assessment. In all other periods, subjects were required to arrive at the clinic at approximately 11 h prior to dosing (i.e., the previous evening). A snack was provided at approximately 21:00 and thereafter subjects were required to fast until 4 h post-dose. Subjects were required to complete the Adult Reading Test. On the morning of each dosing day, each subject's health status was updated and pre-dose procedures (blood pressure and pulse, alcohol and drug of abuse screen and pregnancy test for female subjects) were carried out.

Within the 30 min before dosing started the following pre-dose procedures were carried out: cardiac monitoring was started, blood pressure and pulse recorded, conjunctival reddening assessed and a well-being questionnaire completed. The pre-dose blood sample was also taken.

Blood Sampling for Plasma Concentration Analysis

Blood samples (5 ml) were collected into 5 ml lithium heparin blood tubes via indwelling cannula or individual venipuncture. Samples were placed immediately into an ice bath until centrifuged (1000 G for 10 min at 4°C). The resultant plasma was decanted into two identical pre-labelled amber glass plasma tubes and placed in a freezer at −20°C.

Blood samples were collected pre-dose and at 5, 10, 15, 30 and 45 min and at 1, 2, 3, 4, 6, 8 and 12 h post-dose.

Plasma Concentration Analytical Procedures

Plasma concentrations of CBD, THC and 11-hydroxy-THC were measured in each plasma sample according the analytical protocol.

SAFETY ASSESSMENTS

Urine Drug Screen

Urine drug screens were required to be carried out at check-in for each study period. The drug screen was required to be negative for all drugs pre-dose Period 1. In subsequent periods, positive THC results may have occurred due to administration of test treatment in the previous period and therefore screening for THC was not carried out. The urine sample was required to be negative for all other drugs tested for the subject to be eligible to continue.

Blood Pressure and Pulse

Subjects' blood pressure and pulse were measured pre-dose then at 5, 10, 15, 30 and 45 min and at 1, 2, 3, 4, 6, 8 and 12 h post-dose.

Cardiac Monitoring

Cardiac monitoring was carried out continually from pre-dose to 4 h post-dose for each subject. A print out from the monitor was retained with the study centre study files.

Conjunctival Redness

Subjects were visually assessed for conjunctival reddening at the following times: pre-dose, 15, 30 and 45 min and at 1, 2, 4, 8 and 12 h post-dose. The extent of reddening was scored according to Table 2.

TABLE 2. Conjunctival Reddening Guidelines

Condition	*Score*
No reddening apparent	0
Slight reddening	1
Moderate reddening	2
Severe reddening	3

Adverse Events

Subjects' health was monitored continuously throughout the study. Subjects were also encouraged to inform the clinical staff of any changes in their health as soon as possible. All AEs were recorded in the CRF and followed to resolution or at the discretion of the Investigator.

Cognitive Assessments

Cognitive tests were carried out in Periods 1 to 4 only, using the Cambridge Neuropsychological Test Automated Battery (CANTAB), supplied by CeNeS, Histon, Cambridgeshire, UK. Subjects were asked to complete cognitive tests on the day before dose in Period 1 (baseline), and in each period at 10 min post last actuation then at 3 and 8 h post-dose.

Well-Being Questionnaire

Subjects were required to complete a series of visual analogue scales for alertness, well-being, mood, dryness of mouth, hunger level and any unpleasant effects. These were carried out on Day−1 and then in each period pre-dose, 10 min and 3, 8 and 12 h post-dose.

FOOD AND BEVERAGES

Dietary Restrictions

The subjects were instructed not to consume alcohol or caffeine-containing food or drink from 48 h before dosing in each period until after they were discharged from the clinical unit. During treatment free days

subjects were required to limit their alcohol intake to no more than three units per day (males) or two units per day (females).

A snack was provided at 21:00 on the evening before dosing, thereafter subjects were required to fast until 4 h post-dose. After 4 h post-dose, decaffeinated drinks were provided *ad libitum*. Lunch and dinner were provided at 4 and 9 h post-dose, respectively. Subjects were provided with breakfast prior to discharge at 24 h post-dose. With the exception of the snack at 13 h post-dose and breakfast on Day 2, subjects were required to eat the entire meals provided. The details of diet are presented in Table 3.

Check-Out Procedures

Following breakfast on Day 2 (approximately 24 h post-dose) of each study period and if deemed well enough to leave by the Investigator, subjects were discharged from the clinical unit. Prior to discharge, any ongoing AEs were updated and follow-up arranged if required.

Post-Study Screening

Each subject was required to return to the clinical unit no more than ten days post last dose to undergo a post-study examination. This consisted of a physical examination, blood samples taken for haematology and clinical chemistry, urinalysis, a 12-lead ECG and vital signs recorded. Any ongoing AEs were updated and, if required, arrangements were made to follow up with the subjects.

TABLE 3. Suggested Menu

Meal	*Time*	*Content*
Evening Meal	Day −1, 21:00	Two filled rolls One light desert (e.g., yoghurt) One piece of fruit Decaffeinated drink
Lunch	Day 1, 4 h post-dose	Cooked meal (e.g., meat and two vegetables) Dessert
Evening Snack	Day 1, 13 h post-dose	Optional, no restrictions
Breakfast	Day 2	Optional, no restrictions

DATA QUALITY ASSURANCE

Study Monitoring

All details regarding the study were documented within individual CRFs provided by GW for each subject. All data recorded during the study were checked against source data and for compliance with GCP, internal Standard Operating Procedures (SOPs), working practices and protocol requirements. Monitoring of the study progress and conduct was carried out by the Clinical Department of GW according to GW SOPs and was ongoing throughout the study.

Standardisation of Laboratory Procedures

Analysis of safety bloods (haematology and clinical chemistry) was carried out by Unilabs UK (previously J S Pathology Ltd).

Investigator Responsibilities

The Investigator was responsible for monitoring the study conduct to ensure that the rights of the subject were protected, the reported study data were accurate, complete and verifiable and that the conduct of the study was in compliance with ICH GCP. At the end of the study, the Principal Investigator reviewed and signed each CRF declaring the data to be true and accurate. If corrections were made after review the Investigator acknowledged the changes by re-signing the CRF.

Clinical Data Management

Data were double entered into approved data tables using Microsoft Excel software. Manual checks for missing data and inconsistencies were carried out and queries were raised for any resulting issues.

Once the data were clean, i.e., no outstanding queries, then Quality Control (QC) checks of 100% of the data for a 10% sample of the patients were conducted to make a decision on the acceptability of the data. Any errors were resolved and any error trends across all subjects were also corrected. Upon completion of the QC step, the data sets were burnt onto a compact disc.

Quality Assurance Audits

Clinical Quality Audits were carried out.

Statistical and Analytical Plans

The statistical analysis was carried out as indicated in the protocol. All statistical analyses were performed using SAS® for Windows (v8) software.

Pharmacokinetic Analysis

All p-values quoted are two-sided. No blood samples were missed in the subjects who were dosed therefore all subjects were deemed evaluable for and were included in pharmacokinetic analyses. The pharmacokinetic parameters calculated were as noted in Table 4.

Summary statistics were calculated for each pharmacokinetic parameter and treatment (arithmetic mean, number (N), standard deviation (SD), coefficient of variance (CV%), minimum and maximum for all parameters and additionally the geometric mean for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max}). $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} were natural log transformed prior to analysis and T_{max} was analysed untransformed; $t_{1/2}$ and K_{el} were summarised only. Each parameter was analysed using analysis of variance (ANOVA) with subject and treatment as factors. Least square (LS) means were presented for each test treatment. Point estimates (differences between least square means) for the contrasts between each of High THC, aerosol and inhaler with CBD:THC were presented with the corresponding 95% confidence intervals (CI); for the log-transformed variables, the contrasts were first back transformed to provide ratios and corresponding 95% confidence intervals. The distribution of T_{max} was also summarised.

TABLE 4. Pharmacokinetic Definitions

T_{max}	Time to the maximum measured plasma concentration.
C_{max}	Maximum measured plasma concentration over the time span specified.
$t_{1/2}$	Putative effective elimination half life (the initial descending portion of each plasma concentration-time graph).
$AUC_{0\text{-}t}$	The area under the plasma concentration versus time curve, from time zero to ‘t’ (where t = the final time of positive detection, $t \leq 12h$) as calculated by the linear trapezoidal method.
$AUC_{0\text{-}\infty}$	The area under the plasma concentration versus time curve from zero to t calculated as $AUC_{0\text{-}t}$ plus the extrapolated amount from time t to infinity.
K_{el}	The elimination rate constant.

Pharmacodynamic Analysis

All subjects who completed at least one study period were evaluable for pharmacodynamic analysis. All pharmacodynamic parameters were summarised by test treatment group and analyte. Data for conjunctival reddening and well-being questionnaire were summarised descriptively by time point and treatment (arithmetic means, N, SDs, medians, minima and maxima or counts and percentages, as appropriate). The changes from pre-dosing for the well-being questionnaire were summarised similarly. Analysis of the cognitive assessments was carried out by CeNeS Ltd.

SAFETY ANALYSIS

Adverse Events

All AEs were coded by Medical Dictionary of Regulatory Activities (MedDRA) and presented by system organ class (SOC) and preferred term (PT). Laboratory data collected pre and post-study were summarised descriptively (N, mean, SD, median, minimum and maximum) at each of the two time-points and also as the change from pre-study to post-study.

Blood Pressure and Pulse

For blood pressure and pulse descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change in means from pre-dose. Blood pressure and pulse data are listed for each subject at each time point.

12-Lead ECG

For each of the ECG parameters (heart rate (HR), PR interval, QT interval and QRS width), descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised pre- and post-study.

Determination of Sample Size

No formal sample size calculation was carried out for this study, as it was a “First in man” safety and tolerability study.

Changes in the Conduct of the Study or Planned Analyses

The protocol stated that the pharmacokinetic parameters $AUC_{0\text{-}t}$, C_{max}, C_{res} and T_{max} would be evaluated. In accordance with standard practice, T_{max}, C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ were evaluated and compared between treatments. In addition, $t_{1/2}$ and K_{el} were summarised only.

Study Subjects

Three healthy male and three healthy female subjects were required to complete the study in its entirety. Six male and six female subjects were randomised and all of those subjects completed the study. No subjects withdrew from the study and no replacements were required. Only one minor protocol deviation was reported throughout the study. One subject consumed caffeine in the 48 h prior to dosing for Period 4. This was not considered by the Investigator to affect the subject's eligibility and is not considered to affect the integrity of the study.

Plasma Concentration and Pharmacokinetic Evaluation

Six healthy subjects (three male and three female) were required to complete the study in its entirety. Six subjects (001 to 006) who were randomised in the study were included in the data analysis.

Demographic and Baseline Characteristics

All subjects included in the study complied with all demographic and baseline requirements.

Measurements of Compliance

Each test treatment was administered by suitably trained clinical staff. No deviations to the dosing regimen were noted for any subject throughout the study.

INDIVIDUAL PLASMA CONCENTRATION DATA AND PHARMACOKINETIC RESULTS

Analysis of Plasma Concentration Results

Plasma samples were analysed for CBD, THC and 11-hydroxy-THC according to the analytical protocol. Analytical results were produced

in tabular form and concentration-time graphs were produced from these data. Mean plasma concentrations are summarised in Table 5.

The LLOQ was 1 ng/ml. Data below the LLOQ are presented as <1 and the actual value measured is presented in parenthesis. The actual values measured were used when creating graphs.

CBD:THC Sublingual Drops

Mean concentrations of CBD, THC and 11-hydroxy-THC were above the LLOQ by 45 min post-dose (Figure 1) (range of individual times: 45-180 min, CBD; 30-120 min THC and 11-hydroxy-THC). Mean concentrations of THC (Table 6) were at least double those of CBD throughout the sampling period and from 120 min to the end of sampling mean concentrations of 11-hydroxy-THC were approximately double those of THC (CBD 1.23 ng/ml, THC 3.13 ng/ml, 11-hydroxy-THC 6.68 ng/ml). By 360 and 480 min post-dose the mean level of CBD and THC, respectively and all individual levels were below the LLOQ.

High CBD Sublingual Drops

Mean concentrations of CBD were above the LLOQ by 30 min post-dose (range: 30-120 min), peaked at 120 min (1.49 ng/ml) and

TABLE 5. Mean Plasma Concentration Data

Time (min)	Mean Plasma Concentrations											
	CBD				THC				11-Hydroxy THC			
	CBD: THC SL Drops	High CBD SL Drops	Aerosol	Nebuliser	CBD: THC SL Drops	High THC SL Drops	Aerosol	Nebuliser	CBD: THC SL Drops	High THC SL Drops	Aerosol	Nebuliser
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	0.00	0.00	0.00	6.81	0.00	0.00	0.00	9.45	0.00	0.00	0.00	0.00
10	0.00	0.00	0.00	3.26	0.00	0.00	0.00	5.88	0.00	0.00	0.00	0.26
15	0.00	0.00	0.24	5.04	0.00	0.21	0.23	6.50	0.00	0.00	0.00	0.22
30	0.00	0.33	0.48	5.40	0.19	1.03	1.00	8.25	0.34	1.17	0.72	0.43
45	0.60	0.58	0.96	2.91	1.64	1.71	1.49	4.44	1.70	2.57	1.68	0.24
60	1.20	0.93	0.97	4.56	3.04	3.33	1.87	6.74	3.51	4.36	2.56	0.55
120	1.64	1.49	0.73	0.96	4.67	3.86	2.38	2.31	7.43	5.19	4.84	0.29
180	1.23	0.73	0.86	0.39	3.13	2.94	2.36	0.91	6.68	4.81	5.07	0.20
240	0.48	0.45	0.60	0.29	1.70	1.34	1.38	0.36	4.82	3.14	3.90	0.00
360	0.00	0.00	0.99	0.00	0.55	0.00	1.30	0.00	2.43	1.01	2.89	0.00
480	0.00	0.00	0.22	0.00	0.00	0.00	0.22	0.00	1.05	0.23	1.40	0.00
720	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.00	0.17	0.00

FIGURE 1. GWPD9901: Mean Plasma Cannabinoid Concentrations Following Adminstration of CBD:THC, 1:1 Sublingual Drops

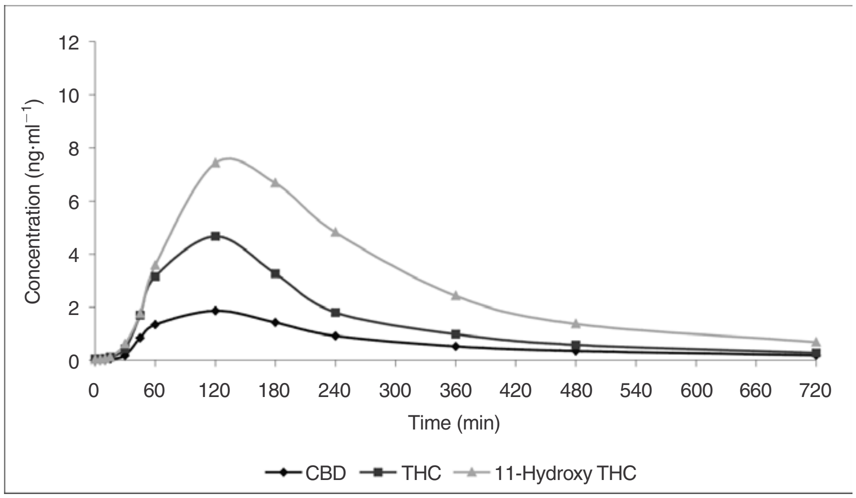


TABLE 6. Mean Pharmacokinetic Parameters

Time (min)	Mean Pharmacokinetic Parameters				
	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (ng/ml.min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (ng/ml.min)
CBD					
CBD:THC SL Drops	100	2.58	209.30	118.33	578.89
High CBD SL Drops	130	2.05	156.13	NC	NC
Aerosol	141	2.60	325.93	143.77	811.75
Nebuliser	36	9.49	564.35	65.71	726.81
THC					
CBD:THC SL Drops	100	6.50	737.48	78.53	928.42
High THC SL Drops	110	5.77	628.80	65.53	818.10
Aerosol	130	3.69	636.11	83.00	776.09
Nebuliser	32	12.46	786.33	47.13	899.77
11-Hydroxy THC					
CBD:THC SL Drops	140	8.25	1842.75	117.68	2066.30
High THC SL Drops	110	7.29	1163.78	99.55	1373.19
Aerosol	160	6.23	1568.20	138.11	1838.04
Nebuliser	38	1.65	65.15	132.56	495.67

NC = Not acceptable

thereafter declined such that they were below the LLOQ by 360 min in all subjects (Figure 2). Mean plasma concentrations of CBD were generally similar to those seen for CBD:THC sublingual drops (Table 6). Neither THC nor 11-hydroxy-THC was detected in quantifiable amounts throughout the sampling period.

High THC Sublingual Drops

Mean concentrations of THC were above the LLOQ by 15 min post-dose (individual range: 15-60 min) (Figure 3), which was marginally earlier than for the CBD:THC sublingual drops (45 min post-dose). Mean concentration reached a peak around 120 min (3.86 ng/ml) (Table 6) and by 360 min had declined below the LLOQ. Mean concentrations of 11-hydroxy-THC were above the LLOQ by 30 min post-dose (individual range: 30-60 min) (Figure 3), which was also marginally earlier than for the CBD:THC sublingual drops (45 min post-dose). Mean concentration reached a peak around 120 min (5.19 ng/ml) and by 480 min had declined below the LLOQ. Concentrations of THC and 11-hydroxy-THC were generally similar to those seen after the CBD:THC sublingual drops.

FIGURE 2. GWPD9901: Mean Plasma Cannabinoid Concentrations Following Administration of High CBD Sublingual Drops

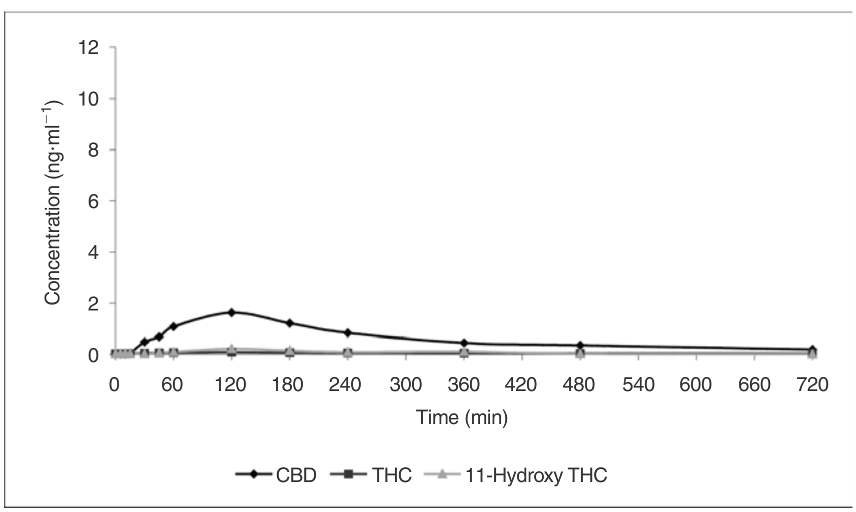
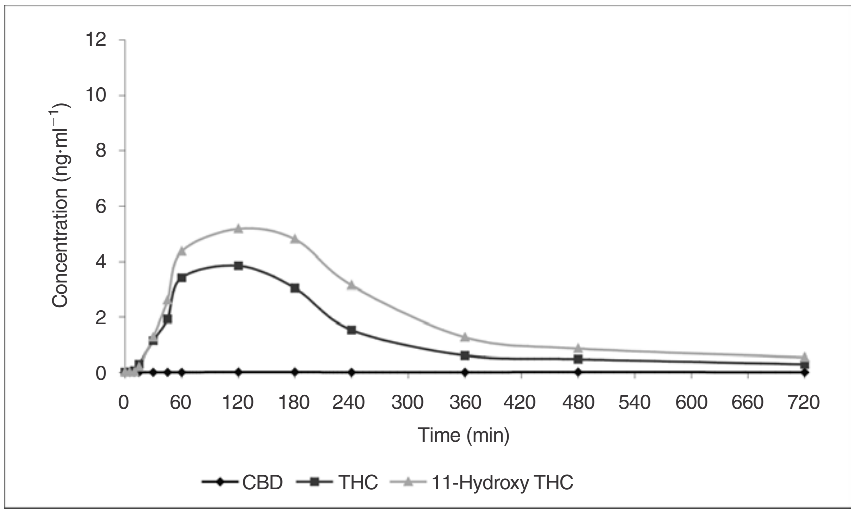


FIGURE 3. GWPD9901: Mean Plasma Cannabinoid Concentrations Following Administration of High THC Sublingual Drops



Placebo Sublingual Drops

Following placebo dosing no quantifiable amount of any cannabinoid was detected in any subject during the sampling period.

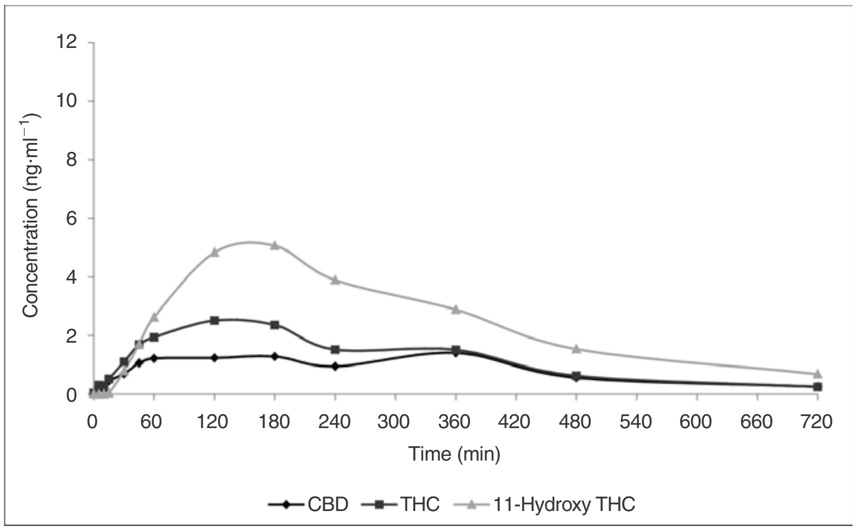
Pressurised Aerosol

Mean concentrations of CBD and THC above the LLOQ were detected in plasma by 15 min post-dose (range 10-180 min for CBD (excepting Subject 006 for whom concentrations remained below LLOQ); 15-180 min for THC) which was marginally earlier than for the CBD:THC sublingual drops (Figure 4).

Mean concentrations of CBD show two similar peak levels at 60 and 360 min (0.97 and 0.99 ng/ml, respectively) (Figure 4) reflecting the variability in the time of peak plasma concentration (range 45-360 min) between individuals. Mean concentrations of CBD had declined below LLOQ by 720 min.

Mean concentrations of THC peaked around 120-180 min (2.38 ng/ml, 2.36 ng/ml) and had declined below LLOQ by 720 min (Figure 4). Mean concentrations of 11-hydroxy-THC above the LLOQ were de-

FIGURE 4. GWPD9901 Extension: Mean Plasma Cannabinoid Concentrations Following Administration of CBD:THC 1:1 Aerosol



tected in plasma by 30 min post-dose (range: 30-120 min), peaked around 180 min (5.07 ng/ml) and then declined more slowly than THC or CBD and remained above the LLOQ at 720 min (Figure 4).

Mean concentrations of THC were generally greater than those for CBD but less than mean concentrations of 11-hydroxy-THC (Table 6). Mean concentrations of CBD, THC and 11-hydroxy-THC following the pressurised aerosol were generally higher than for the CBD:THC sublingual drops from 45-60 min to 240 min and were lower than for the CBD:THC sublingual drops at almost all other time points. At 360 min to 720 min post-dose mean concentrations of each cannabinoid were marginally greater for the pressurised aerosol than for the CBD:THC sublingual drops.

Following administration of the test treatment via the pressurised aerosol, mean concentrations of each cannabinoid in plasma were above the LLOQ for longer when compared to the CBD:THC sublingual drops.

Inhaled Nebuliser

The dose administered via the inhaled nebuliser was approximately half that of the sublingual drops and aerosol. Mean concentrations of

CBD and THC were above the LLOQ by 5 min post-dose (range 5-30 min for both CBD and THC) and each cannabinoid was detected in plasma notably earlier than the CBD:THC sublingual drops (Figure 5).

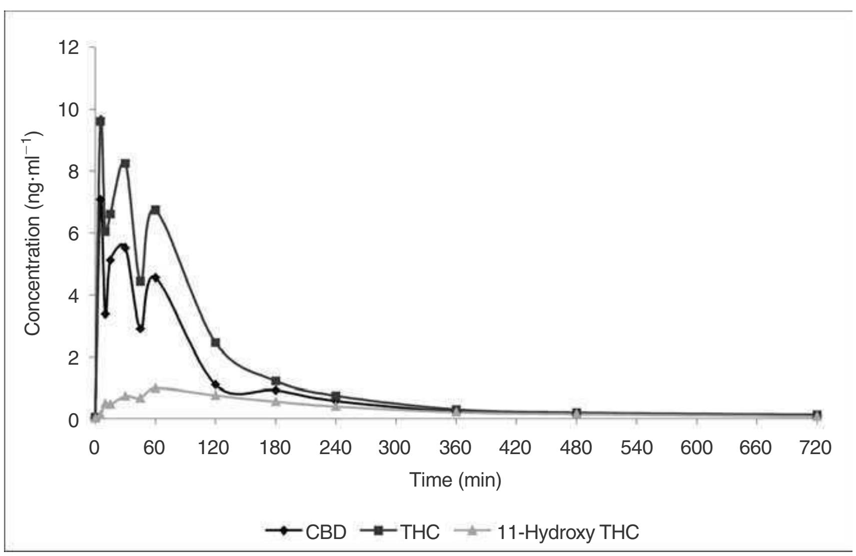
Mean concentrations of CBD fluctuated considerably between 5 min and 60 min post-dose, reflecting the variability in levels and timing of peak concentrations in individuals, but were considerably higher than following the other treatments.

Mean concentrations of THC were higher than corresponding concentrations of CBD and also fluctuated considerably between 5 min and 60 min post-dose, reflecting the individual variability.

Mean concentrations of both CBD and THC declined rapidly from 60 min. CBD concentrations were below the LLOQ in all but one subject at 180 min and THC in all but one subject by 240 min.

Mean concentrations of 11-hydroxy-THC were much lower than corresponding concentrations of both CBD and THC and much less than following the other treatments (Figure 5). In three subjects, levels of 11-hydroxy-THC failed to rise above the LLOQ at all during the sampling period.

FIGURE 5. GWPD9901 Extension: Mean Plasma Cannabinoid Concentrations Following Administration of CBD:THC, 1:1 Nebuliser



Analysis of Pharmacokinetic Parameters

PK parameters were calculated using WinNonlin® Professional 3.1. The model used was a non-compartmental, linear trapezoidal analysis. Values below the LLOQ were not used when calculating PK parameters. Mean values are presented in (Table 6).

The PK parameters for each test treatment (with the exception of placebo) were statistically compared to the PK parameters for the CBD:THC sublingual drops. Due to the low concentrations of cannabinoids in plasma some individual PK parameters were not calculable and therefore some of the mean PK parameters are not based on all six subjects.

CBD:THC Sublingual Drops

Following the CBD:THC sublingual drops arithmetic mean T_{max} of CBD (Table 7) and THC (Table 8) was 100 and 100 min, respectively. Arithmetic mean C_{max} of CBD was 2.58 ng/ml, arithmetic mean $AUC_{0\text{-}t}$ 209.3 ng/ml.min and $AUC_{0\text{-}\infty}$ 578.89 ng/ml.min. The corresponding values for THC were greater as C_{max} was 6.50 ng/ml, $AUC_{0\text{-}t}$ 737.48 ng/ml.min and $AUC_{0\text{-}\infty}$ 928.42 ng/ml.min. The arithmetic mean T_{max} of 11-hydroxy-THC was 140 min (Table 9). Arithmetic mean C_{max} was 8.25 ng/ml, arithmetic mean $AUC_{0\text{-}t}$ 1842.75 ng/ml.min and $AUC_{0\text{-}\infty}$ 2066.30 ng/ml.min.

High CBD Sublingual Drops

The mean PK parameters for CBD following administration of High CBD sublingual drops were not statistically significantly different from

TABLE 7. CBD Pharmacokinetic Parameters: CBD:THC Sublingual Drops

Subject	*T_{max} (min)*	*C_{max} (ng/ml)*	*$AUC_{0\text{-}t}$ (min*ng/ml)*	*K_{el} (1/min)*	*$t_{1/2}$ (min)*	*$AUC_{0\text{-}\infty}$ (min*ng/ml)*
1	120	3.70	264.00	NC	NC	NC
2	60	2.63	449.18	0.0048	144.57	749.51
3	60	1.95	14.63	NC	NC	NC
4	180	2.75	208.50	NC	NC	NC
5	60	2.64	266.10	0.0075	92.10	408.27
6	120	1.78	53.40	NC	NC	NC
Mean	100	2.58	209.30	0.0062	118.33	578.89
SD**	60-180	0.68	158.72	0.0019	37.10	241.29

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 8. THC Pharmacokinetic Parameters: CBD:THC Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	120	9.29	880.28	0.0157	44.28	971.00
2	60	6.44	1005.75	0.0076	90.62	1327.35
3	60	5.62	287.85	0.0218	31.80	357.60
4	180	6.31	916.20	0.0077	89.71	1118.09
5	60	4.93	549.98	0.0083	83.77	686.54
6	120	6.38	784.80	0.0053	131.02	1109.93
Mean	100	6.50	737.48	0.0111	78.53	928.42
SD**	60-180	1.49	269.76	0.0063	35.81	350.49

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 9. 11-Hydroxy THC Pharmacokinetic Parameters: CBD:THC Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	120	12.14	2459.40	0.0089	78.21	2586.89
2	180	7.87	1996.05	0.0060	115.20	2205.45
3	60	6.52	1208.85	0.0075	92.51	1343.65
4	240	7.22	2371.80	0.0045	153.34	2635.06
5	120	6.95	1459.20	0.0057	122.16	1758.81
6	120	8.82	1561.20	0.0048	144.64	1867.94
Mean	140	8.25	1842.75	0.0062	117.68	2066.30
SD**	60-240	2.07	512.22	0.0017	29.04	503.98

** T_{max} presented as minimum-maximum
NC = Not calculable

the CBD:THC sublingual drops (Table 10). The arithmetic mean T_{max} was 130 min and arithmetic mean C_{max} 2.05 ng/ml, arithmetic mean AUC_{0-t} was numerically lower than following the CBD:THC sublingual drops at 156.13 ng/ml.min. $AUC_{0-\infty}$ was not calculable as there were generally few time points in any subjects when plasma levels of CBD exceeded the LLOQ (at a single sampling time in three subjects).

High THC Sublingual Drops

Only mean $AUC_{0-\infty}$ for 11-hydroxy-THC following administration of the High THC sublingual drops (Table 11) was statistically signifi-

TABLE 10. CBD Pharmacokinetic Parameters: High CBD Sublingual Drops

Subject	T_{max} *(min)*	C_{max} *(ng/ml)*	$AUC_{0\text{-}t}$ *(min*ng/ml)*	K_{el} *(1/min)*	$t_{1/2}$ *(min)*	$AUC_{0\text{-}\infty}$ *(min*ng/ml)*
1	240	1.32	185.40	NC	NC	NC
2	120	3.17	563.03	0.0135	51.18	664.93
3	120	1.90	57.00	NC	NC	NC
4	60	3.21	49.73	NC	NC	NC
5	120	1.14	34.20	NC	NC	NC
6	120	1.58	47.40	NC	NC	NC
Mean	130	2.05	156.13	NC	NC	NC
SD**	60-240	0.92	207.01	NC	NC	NC

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 11. 11-Hydroxy THC Pharmacokinetic Parameters: High THC Sublingual Drops

Subject	T_{max} *(min)*	C_{max} *(ng/ml)*	$AUC_{0\text{-}t}$ *(min*ng/ml)*	K_{el} *(1/min)*	$t_{1/2}$ *(min)*	$AUC_{0\text{-}\infty}$ *(min*ng/ml)*
1	120	6.74	1105.05	0.0070	98.38	1261.17
2	120	7.97	1793.18	0.0072	96.32	1983.56
3	60	6.21	669.83	0.0055	126.84	944.30
4	180	7.83	1292.70	0.0091	76.32	1456.75
5	120	6.67	1205.63	0.0065	105.95	1441.02
6	60	8.31	916.28	0.0074	93.49	1152.32
Mean	110	7.29	1163.78	0.0071	99.55	1373.19
SD**	60-180	0.85	380.32	0.0012	16.58	354.80

** T_{max} presented as minimum-maximum
NC = Not calculable

cantly lower when compared to the CBD:THC sublingual drops (1373.19 ng/ml.min vs. 2066.30 ng/ml.min, p = 0.0358). For THC (Table 12), T_{max} was 110 min, C_{max} 5.77 ng/ml, $AUC_{0\text{-}t}$ 628.80 ng/ml and $AUC_{0\text{-}\infty}$ 818.10 ng/ml. $C_{max,}$ $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were slightly lower than following the CBD:THC sublingual drops and T_{max} was slightly later but these differences were not statistically significant.

Pressurised Aerosol

There were no statistically significant differences in PK parameters for CBD (Table 13), THC (Table 14) or 11-hydroxy-THC (Table 15)

TABLE 12. THC Pharmacokinetic Parameters: High THC Sublingual Drops

Subject	*T_{max} (min)*	*C_{max} (ng/ml)*	*$AUC_{0\text{-}t}$ (min*ng/ml)*	*K_{el} (1/min)*	*$t_{1/2}$ (min)*	*$AUC_{0\text{-}\infty}$ (min*ng/ml)*
1	120	5.46	708.45	0.0083	83.65	952.23
2	120	4.84	747.68	0.0047	146.19	1325.57
3	60	4.25	262.68	0.0238	29.14	305.56
4	180	7.75	937.20	0.0226	30.70	1025.79
5	120	6.76	727.95	0.0139	49.75	819.10
6	60	5.55	388.88	0.0129	53.72	480.33
Mean	110	5.77	628.80	0.0144	65.53	818.10
SD**	60-120	1.28	251.80	0.0076	44.18	372.95

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 13. CBD Pharmacokinetic Parameters: Pressurised Aerosol

Subject	*T_{max} (min)*	*C_{max} (ng/ml)*	*$AUC_{0\text{-}t}$ (min*ng/ml)*	*K_{el} (1/min)*	*$t_{1/2}$ (min)*	*$AUC_{0\text{-}\infty}$ (min*ng/ml)*
1	45	1.38	179.85	NC	NC	NC
2	120	2.76	536.85	0.0082	84.39	665.90
3	60	2.39	81.18	NC	NC	NC
4	360	4.85	940.80	0.0108	63.92	1062.52
5	120	1.61	216.90	0.0024	283.00	706.84
6	NC	NC	0.00	NC	NC	NC
Mean	141	2.60	325.93	0.0071	143.77	811.75
SD**	45-360	1.38	352.68	0.0043	121.01	218.13

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 14. THC Pharmacokinetic Parameters: Pressurised Aerosol

Subject	*T_{max} (min)*	*C_{max} (ng/ml)*	*$AUC_{0\text{-}t}$ (min*ng/ml)*	*K_{el} (1/min)*	*$t_{1/2}$ (min)*	*$AUC_{0\text{-}\infty}$ (min*ng/ml)*
1	180	2.43	500.10	0.0143	48.45	570.00
2	120	4.66	814.95	0.0152	45.55	888.55
3	60	3.72	356.60	0.0101	68.78	466.74
4	180	4.64	1139.40	0.0105	66.28	1263.71
5	120	3.04	377.03	0.0068	101.54	573.32
6	120	3.67	628.58	0.0041	167.41	894.25
Mean	130	3.69	636.11	0.0102	83.00	776.09
SD**	60-180	0.88	299.70	0.0043	45.93	297.88

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 15. 11-Hydroxy THC Pharmacokinetic Parameters: Pressurised Aerosol

Subject	*T_{max} (min)*	*C_{max} (ng/ml)*	*AUC_{0-t} (min*ng/ml)*	*K_{el} (1/min)*	*$t_{1/2}$ (min)*	*$AUC_{0-\infty}$ (min*ng/ml)*
1	180	4.32	820.43	0.0107	65.08	958.44
2	120	6.08	1380.68	0.0046	149.66	1639.78
3	60	6.03	1726.43	0.0046	149.78	2082.97
4	360	6.54	2290.50	0.0050	137.48	2490.83
5	120	7.10	1316.03	0.0043	160.82	1550.36
6	120	7.30	1875.15	0.0042	165.86	2305.87
Mean	160	6.23	1568.20	0.0056	138.11	1838.04
SD**	60-360	1.07	509.69	0.0025	37.12	565.82

** T_{max} presented as minimum-maximum
NC = Not calculable

between the pressurised aerosol and CBD:THC sublingual drops. Following dosing with the pressurised aerosol T_{max} of both CBD and THC were a little later than after dosing with the CBD:THC sublingual drops (CBD 141 vs. 100 min and THC 130 vs. 100 min). CBD C_{max}, was very similar but AUC_{0-t} and $AUC_{0-\infty}$ were greater than following CBD:THC sublingual drops whereas THC $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ were all less than the sublingual drops. None of these differences was statistically significant.

Inhaled Nebuliser

The dose administered via the inhaled nebuliser was approximately half that of the sublingual drops and aerosol. T_{max}, of both CBD (36 min) (Table 16) and THC (32 min) (Table 17) were much earlier than the corresponding values after the sublingual drops (100 min and 100 min, respectively) or aerosol (T_{max} THC = 130 min, CBD = 141 min), though only the difference in THC T_{max} was significant for sublingual drops ($p = 0.0046$). Mean C_{max} of CBD (9.49 ng/ml) was statistically significantly greater than for the CBD:THC sublingual drops (2.58 ng/ml) ($p = 0.0104$). Mean C_{max} of THC was similarly greater (12.46 vs. 6.5 ng/ml) though the difference was not statistically significant. Mean AUC_{0-t} of CBD (564.35 ng/ml.min) was greater than for the CBD:THC sublingual drops (209.30 ng/ml.min); however, with a p-value of 0.0529, this was not a statistically significant difference. The AUC_{0-t} and $AUC_{0-\infty}$ values for CBD following dosing with the inhaled nebuliser were greater, though not statistically significantly, than the correspond-

TABLE 16. CBD Pharmacokinetic Parameters: Nebuliser

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	5	22.62	442.55	0.0275	25.23	479.68
2	30	9.87	499.53	0.0166	41.70	587.36
3	45	2.74	219.60	0.0039	179.66	750.96
4	15	4.70	171.20	0.0278	24.92	235.20
5	60	14.75	1859.90	0.0124	55.69	1997.28
6	60	2.25	193.33	0.0103	67.05	310.36
Mean	36	9.49	564.35	0.0164	65.71	726.81
SD**	5-60	8.01	649.39	0.0096	58.25	649.66

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 17. THC Pharmacokinetic Parameters: Nebuliser

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	5	25.85	633.30	0.0334	20.74	675.50
2	30	14.74	884.58	0.0144	48.18	963.81
3	60	3.73	449.63	0.0089	77.77	593.24
4	30	5.15	217.35	0.0191	36.21	368.84
5	5	21.97	2256.68	0.0164	42.21	2387.60
6	60	3.29	276.48	0.0120	57.69	409.64
Mean	32	12.46	786.33	0.0174	47.13	899.77
SD**	5-60	9.89	760.53	0.0086	19.45	759.49

** T_{max} presented as minimum-maximum
NC = Not calculable

ing values for CBD:THC sublingual drops. $AUC_{0-\infty}$, AUC_{0-t}, C_{max} and T_{max} for 11-hydroxy-THC (495.67 ng/ml.min, 65.15 ng/ml.min, 1.65 ng/ml and 38 min, respectively) (Table 18) were statistically significantly lower when compared to the CBD:THC sublingual drops (2066.30 ng/ml.min, 1842.75 ng/ml.min, 8.25 ng/ml and 140 min, respectively). The p-values were 0.0034, < 0.0001, < 0.0001 and 0.0054, respectively.

Analysis of Cognitive Assessments and Well-Being

For each test treatment period, subjects were required to undertake a battery of cognitive assessments (Periods 1 to 4 only) and complete a well-being questionnaire. Subjects were also required to report a series

TABLE 18. 11-Hydroxy THC Pharmacokinetic Parameters: Nebuliser

Subject	T_{max} *(min)*	C_{max} *(ng/ml)*	$AUC_{0\text{-}t}$ *(min*ng/ml)*	K_{el} *(1/min)*	$t_{1/2}$ *(min)*	$AUC_{0\text{-}\infty}$ *(min*ng/ml)*
1	10	1.56	30.10	NC	NC	NC
2	45	1.18	25.65	NC	NC	NC
3	NC	NC	0.00	NC	NC	NC
4	NC	NC	0.00	NC	NC	NC
5	60	2.21	270.00	0.0052	132.56	495.67
6	NC	NC	NC	NC	NC	NC
Mean	38	1.65	65.15	0.0052	132.56	495.67
SD**	10-60	0.52	115.37	NC	NC	NC

** T_{max} presented as minimum-maximum
NC = Not calculable

of well-being parameters using visual analogue scales (VAS). Each pre-dose assessment was taken to be the baseline measurement for each well-being parameter for each period.

Wakefulness was rated (0 = very drowsy and 100 = fully alert). CBD:THC sublingual drops resulted in the greatest drop in feeling of wakefulness with a decrease in wakefulness of −32.5 from baseline (88.5) at 3 h post-dose. All other test treatments, with the exception of placebo, which showed increased wakefulness throughout, also showed the greatest effect on wakefulness at 3 h post-dose with a range of decreases of −11.5 (High CBD) to −20.2 (aerosol).

Well-being was rated (0 = feel terrible and 100 = feel wonderful). Each test treatment resulted in a reduction similar to that for placebo in feeling of well-being. The greatest reduction (14.2 relative to baseline (94.0) at 3 h post-dose) was as a result of the CBD:THC sublingual drops. High CBD resulted in a later (−4.0 relative to baseline at 8 h post-dose) maximum mean decrease and the aerosol test treatment resulted in an earlier (−2.3 relative to baseline at 10 min post-dose) maximum mean decrease.

Mood was rated (0 = feel terrible and 100 = feel wonderful). All test treatments resulted in a maximum mean decrease (−2.2 to −11.3 relative to baseline) in mood at 3 h post-dose with the exception of the aerosol test treatment which showed a maximum mean decrease (2.7 relative to baseline) at 8 h post-dose.

Dry mouth was rated (0 = very dry and 100 = normal moisture). All test treatments, with the exception of the inhaler, resulted in a maximum mean increase in reporting of dry mouth at 3 h post-dose. CBD:THC

sublingual drops resulted in the greatest increase in dryness of mouth with a maximum mean of −48.7 relative to baseline. The nebuliser test treatment resulted in an earlier maximum mean decrease with a change of −10.8 (relative to baseline) at 10 min post-dose.

Hunger was rated (0 = very hungry and 100 = not hungry). All test treatments and placebo resulted in a maximum mean increase in reported feeling of hunger at 3 h post-dose. The range of change from baseline was −9.8 (CBD:THC sublingual drops) to −27.5 (aerosol). The maximum mean increase in hunger following the placebo dose was −16.0.

Unpleasant effects were rated (0 = very unpleasant effects and 100 = no unpleasant effects). The maximum mean (relative to baseline) reporting of unpleasant effects was varied for each test treatment. CBD:THC sublingual drops was −11.5 at 3 h post-dose, High CBD was −9.3 at 12 h post-dose, High THC was −4.5 at 10 min post-dose, the aerosol was −5.7 at 8 h post-dose and the nebuliser was −14.0 at 10 min post-dose. The placebo treatment also resulted in reporting of unpleasant effects with a maximum mean increase of −6.5 at 10 min post-dose.

Post-Study Questionnaire

The results of the post-study questionnaire were assessed descriptively using frequency tables for each treatment. All of the subjects reported that the test treatment liked best was the 'liquid under the tongue' and the least liked test treatment was the nebuliser. Half of the subjects reported that the CBD:THC sublingual drops had the most pleasant effects and 67% (4) of the subjects reported that the nebuliser had the least pleasant effects. All of the subjects reported coughing and half reported a sore throat after administration of the test treatment via the nebuliser.

Analysis of Safety Parameters

The output from the cardiac monitors was intended for use at the clinical unit as an ongoing assessment for each subject. No concerns were raised as a result of the cardiac monitoring.

Pre-dose, all test treatments, including placebo but with the exception of High CBD, had between one and three subjects (17-50%) reported as having slight conjunctival reddening. Pre-dose High CBD, no conjunctival reddening was reported. Post-dose for all test treatments including placebo, the majority of subjects (67-100%) were reported as having 'slight' or 'no' conjunctival reddening. With the exception of

High CBD, moderate conjunctival reddening was reported in a maximum of two subjects (33% between 31 min and 4 h 01 min) for all test treatments including placebo. Only one subject had severe conjunctival reddening (on CBD:THC sublingual drops at 4 h 01 min).

Blood Pressure and Pulse During Treatment Periods

For each of the BP and pulse, parameters descriptive statistics (N, mean, SD, median, minimum and maximum) and the changes from pre-dose baseline were presented at each time point by test treatment group. In addition, the summaries were assessed for the absolute change from pre-dose.

12-Lead ECG

The ECG assessments (normal/abnormal) were assessed pre- and post-study.

Drug Dose, Drug Concentration and Relationships to Response

Each subject received three single doses of CBD:THC (20 mg CBD + 20 mg THC), one single dose of High THC (20 mg THC) and one single dose of High CBD (20 mg High CBD) (Table 19). The maximum total dose that was planned to be administered in the study was 80 mg CBD and 80 mg THC.

Drug-Drug and Drug-Disease Interactions

This study was carried out in healthy subjects who were not taking any medication.

Plasma Concentration Conclusions

Sublingual Drops

Following co-administration of CBD and THC as sublingual drops, mean concentrations of CBD, THC and 11-hydroxy-THC were above the LLOQ by 45 min post-dose. Plasma concentrations of THC were at least double those of CBD before both decreased below the LLOQ by 360 min and 480 min post-dose, respectively.

When High CBD sublingual drops were administered, plasma levels of CBD were generally similar to those measured after CBD:THC sublingual drops.

TABLE 19. Total Dose of Test Treatment Administered to Each Subject

Subject	Test Treatment					
	CBD:THC SL Drops	Placebo	High CBD SL Drops	High THC SL Drops	Aerosol	Nebuliser
1	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
2	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
3	12.5 mg CBD + 12.5 mg THC	0 mg	20 mg CBD	15 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
4	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
5	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	0 mg**
6	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	0 mg**

** Subjects 005 and 006 received a placebo dose via the nebuliser

High THC resulted in mean levels of both THC and 11-hydroxy-THC being above the LLOQ earlier and also resulted in a slightly earlier decline than for CBD:THC. However, the concentrations of THC and 11-hydroxy-THC in plasma were similar or a little lower.

Pressurised Aerosol

Following administration of CBD:THC via the pressurised aerosol, mean levels of CBD and THC above the LLOQ were detected a little earlier than for the CBD:THC sublingual drops and declined below the LLOQ a little later. Plasma concentrations of THC, 11-hydroxy-THC and CBD were lower than following the sublingual drops.

Nebuliser

Following a dose administration of CBME via the nebuliser of approximately half that of the sublingual drops, mean plasma levels of both CBD and THC rose rapidly (within 5 min) to levels much higher than measured following sublingual drops and were maintained until around 120 min post-dose before declining rapidly. Levels of 11-hydroxy-THC were very low compared with those after sublingual dosing.

In conclusion, following sublingual administrations of CBD alone, THC alone or CBD:THC combined there was little difference in the plasma concentrations of THC or CBD. However, plasma levels of

CBD are less than corresponding levels of THC suggesting lower bioavailability. Following administration of CBD and THC by pressurised aerosol blood levels of both THC and CBD were lower compared with the sublingual drops. Following administration of CBD and THC via the nebuliser, there was rapid absorption and much greater plasma levels of both CBD and THC compared with sublingual dosing and the low levels of 11-hydroxy-THC suggests that metabolism of THC was significantly reduced.

Pharmacokinetic Conclusions

There were no statistically significant differences in the PK of THC or CBD between CBD:THC sublingual drops and High THC, High CBD or pressurised aerosol. With the exception of a single statistically significant difference in $AUC_{0-\infty}$ for 11-hydroxy-THC following administration of the High THC compared with CBD:THC sublingual drops there were no significant differences in the PK of 11-hydroxy-THC either. The differences in plasma concentrations and mean PK parameters observed between some of these treatments in the study were small relative to the individual variability.

Dosing with the inhaled nebuliser produced marked differences in the PK of CBD and THC compared with CBD:THC sublingual dosing. Peak concentration was greater and much earlier although only C_{max} of CBD and T_{max} of THC were statistically significantly different. Peak concentration and AUCs of 11-hydroxy-THC were statistically significantly less, reflecting reduced early metabolism of THC by this route.

In conclusion, no consistent statistically significant differences were noted between the PK parameters of High CBD, High THC and the aerosol when compared to the CBD:THC sublingual drops. However, the nebuliser resulted in a rapid absorption of CBD and THC and higher peak plasma levels but a reduction in the metabolism of THC to 11-hydroxy-THC.

Well-Being Conclusions

Results indicate that subjects experienced changes in wakefulness, feeling of well-being, mood, production of saliva and increased hunger and unpleasant effect. These were not clinically different following administration of each test treatment or placebo. The maximum mean reduction in wakefulness, feeling of well-being, mood and production of

saliva were reported at 3 h post-dose and were as a result of CBD:THC sublingual drops.

Only small insignificant changes in wakefulness, feeling of well-being and mood were reported following administration of the placebo test treatment. However, a similar decrease in production of saliva, increase in hunger and marginally smaller incidence of unpleasant effects were seen with CBD:THC sublingual drops.

The greatest mean increase in hunger was reported following administration of the aerosol test treatment at 3 h post-dose. However, a similar effect was also observed at 3 h post-dose following administration of the placebo test treatment.

The greatest mean incidence of unpleasant effects was reported earlier than for any other effect and following administration of the nebuliser test treatment.

In conclusion, the decrease in general feeling of well-being were greatest following administration of CBD:THC sublingual drops.

Post-Study Questionnaire Conclusions

The sublingual test treatments were best liked and the nebuliser test treatment was least liked. The effects experienced following test treatment administration via the nebuliser were least liked. All of the subjects reported coughing and three subjects reported a sore throat following dosing during dosing with the nebuliser.

SAFETY EVALUATION

All six subjects completed all six periods of study treatment. The actual doses administered are presented in Table 19.

ADVERSE EVENTS

Brief Summary of Adverse Events

All six subjects experienced at least two AEs each during the study (Table 20). All the AEs were non-serious and most (32 events) were related to the study treatment. The majority of AEs were mild or moderate in intensity and only three AEs were severe. Only one AE was persisting at the end of the study, and most of the events that resolved did so

TABLE 20. Number and Severity of AEs by Test Treatment

Test Treatment	Number and Severity of AEs			Total
	Mild	Moderate	Severe	
THC:CBD SL drops	3	6	2	11
High CBD SL drops	1	4	1	6
High THC SL drops	5	6	0	11
Placebo	1	2	0	3
Aerosol	4	4	0	8
Nebuliser	1	5	0	6
Total	15	27	3	45

without treatment (35 events). The AEs experienced were abnormal dreams, conjunctival hyperaemia, tachycardia, pallor, sleep disorder, increased sweating, hot flushes, hyperacusis, upper abdominal pain, frequent bowel movements, increased body temperature, hunger, depressed mood, cough and hypotension.

Table 20 summarises the number and severity of AEs by test treatment.

Analysis of Adverse Events

All six subjects experienced at least two AEs each during the study. All the AEs were non-serious. Most AEs were related to the study treatment in the active groups, but more AEs were unrelated to treatment in the placebo group. The majority of AEs were mild or moderate in intensity. Only three AEs out of a total of 45 were severe and occurred when the subjects were receiving CBD:THC sublingual drops (conjunctival hyperaemia and hunger) and High CBD sublingual drops (conjunctival hyperaemia). Only one AE was persisting at the end of the study (menopausal symptoms in a 43-year-old female subject, not related to treatment), and most of the events that resolved did so without treatment.

Although the number of patients was small, there were differences between the active study treatments and placebo. Only one subject developed an AE following administration of placebo whereas three to four subjects developed AEs following administration of the active test treatments. Tachycardia, conjunctival hyperaemia and abnormal dreams were the most common AEs experienced and accounted for three, five and eight AEs, respectively, across all treatment groups. Tachycardia

was the most common AE in subjects receiving High THC sublingual drops (two subjects); conjunctival hyperaemia was the most common AE in subjects receiving CBD:THC sublingual drops (two subjects); and abnormal dreams was the most common AE in subjects receiving the aerosol (two subjects) and the inhaler (two subjects). Conjunctival hyperaemia and abnormal dreams were the jointly the most common AEs in subjects receiving the nebuliser.

Abnormal dreams was the only intoxication-type AE developed by the subjects during this study. At least one subject developed them while receiving any one of the test treatments (including placebo), and four subjects developed them overall. Apart from one subject who experienced a cough during the use of the inhaler, no subjects developed any AEs that may have been related to application of the test treatment. There were no deaths, SAEs or other significant AEs during this study.

CLINICAL LABORATORY EVALUATION

Laboratory Values Over Time

The mean value of each laboratory parameter exhibited only small variations from screening to post-study. The small variations did not suggest any patterns or trends.

Individual Subject Changes

Shift tables showed no more than two shifts between categories (low, normal and high) per parameter. The small number of changes did not suggest any patterns or trends.

Individual Clinically Significant Abnormalities

There were no clinically significant abnormalities in the laboratory parameters for any subject at either screening or post-study. Subject 002's urine was positive for nitrites at screening which was considered to be a clinically relevant abnormal result. There were no other clinically relevant abnormal results.

Vital Signs, Physical Findings and Other Observations Related to Safety

The mean values of all the vital signs showed no patterns or trends and no differences from placebo. ECGs at both screening and post-study were normal for all subjects.

Conjunctival Reddening

All test treatments, including placebo but with the exception of High CBD, had a reported incidence of 17-50% of slight conjunctival reddening pre-dose. Pre-dose High CBD, no conjunctival reddening was reported. Post-dose for all test treatments including placebo, the majority of subjects (67-100%) were reported as having 'slight' or 'no' conjunctival reddening. With the exception of High CBD, moderate conjunctival reddening was reported in a maximum of two subjects (33% between 31 min and 4 h 01 min) for all test treatments including placebo. Only CBD:THC sublingual drops resulted in one subject having severe conjunctival reddening at 4 h 01 min.

Safety Conclusions

The sublingual test treatments were well tolerated by all subjects. Each of the 6 subjects experienced at least two non-serious AEs during the study, but there were no deaths, SAEs or other significant AEs. There were a total of 45 AEs, the vast majority of which were mild or moderate in intensity, only three being severe. All but one AE resolved (non-related), most (35) without treatment. Most AEs were related to the study treatment, except for subjects receiving placebo where more AEs were unrelated to treatment.

The commonest AEs were abnormal dreams, conjunctival hyperaemia and tachycardia. Abnormal dreams was the only intoxication-type AE developed by the subjects during this study and was the most common AE overall. No subjects developed any AEs that may have been related to administration of the sublingual test treatments.

The small variations in individual subject laboratory parameters and urinalyses and in the mean laboratory parameters did not suggest any patterns or trends. The mean values of all the vital signs showed no patterns or trends either and no differences from placebo. ECGs at both screening and post-study were normal for all subjects.

DISCUSSION AND OVERALL CONCLUSIONS

The sublingual test treatments were well tolerated at the doses administered by all subjects. All six subjects experienced at least two non-serious AEs during the study, but there were no deaths, SAEs or other significant AEs. All but one AE resolved without treatment. Although the number of AEs was small, subjects clearly developed more AEs when receiving the active test treatment than when receiving placebo.

No overall statistically significantly different differences were reported between each of sublingual test treatments when compared to the CBD:THC sublingual drops. However, there were few subjects in this study and due to the low concentrations of cannabinoids in plasma some PK parameters could not be calculated for some subjects.

When CBD and THC are co-administered as sublingual drops, the rate of appearance of THC is marginally increased compared to being administered as High THC suggesting that CBD may stimulate the absorption of THC. The appearance of 11-hydroxy-THC is reduced when CBD and THC are co-administered suggesting that the metabolism of THC to 11-hydroxy-THC may be reduced by CBD. THC is more extensively absorbed than CBD and no changes were seen for any sublingual drop test treatments relative to CBD:THC sublingual drops.

Administration of CBD:THC via the pressurised aerosol resulted in a slightly faster rate of absorption of CBD and THC than for the CBD:THC sublingual drops. However, overall AUCs were reduced for THC and 11-hydroxy-THC and increased for CBD.

The nebuliser resulted in a very rapid rate and relatively large extent of absorption of both CBD and THC. However it also resulted in the greatest number of adverse effects experienced by the subjects. Administration of the test treatment via the nebuliser was considered practical however, the concept of administering the test treatment via the lungs was shown to be more effective than for sublingual administration. Very low concentrations of 11-hydroxy-THC were produced following nebuliser administration indicating a reduction in metabolism of THC to 11-hydroxy-THC.

Each test treatment resulted in a reduction in subjectively assessed general well-being with the greatest effects reported following administration of CBD:THC sublingual drops. Maximum effects were experienced at approximately the same time post each dose and some effects were also reported following administration of placebo. This suggests that some of the changes in feeling of well being may be due to the excipients or a placebo effect.

The reported increase in hunger following administration of each test treatment was not unexpected as maximum hunger was reported close to lunch time. The greatest mean incidence of unpleasant effects was reported earlier than for any other effect and following administration of the nebuliser test treatment.

In conclusion, each sublingual test treatment was well tolerated by all subjects. The inhaled test treatment was not well tolerated and resulted in adverse effects.

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A Phase I, Open Label, Four-Way Crossover Study to Compare the Pharmacokinetic Profiles of a Single Dose of 20 mg of a Cannabis Based Medicine Extract (CBME) Administered on 3 Different Areas of the Buccal Mucosa and to Investigate the Pharmacokinetics of CBME *per Oral* in Healthy Male and Female Volunteers (GWPK0112)

G. W. Guy
P. J. Robson

SUMMARY. This Phase I, open label, four-way crossover study pertains to pharmacokinetic parameters of four cannabis based medicine extracts (CBME). Sublingual, buccal and oro-pharyngeal test treatments

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G. W. Guy and P. J. Robson are affiliated with GW Pharmaceuticals plc, Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, UK.

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(GW-1000-02) consisted of 25 mg cannabidiol (CBD) + 25 mg Δ^9-tetrahydrocannabinol (THC) per ml formulated in ethanol (eth):propylene glycol (PG) (50:50), with peppermint flavouring with a 100 µl actuation volume (total dose 10 mg CBD + 10 mg THC in 4 actuations). An oral capsule contained 2.5 mg CBD + 2.5 mg THC sprayed onto granulated lactose and encapsulated in soft gelatin capsules (total dose of 10 mg CBD + 10 mg THC 4 capsules). This study was performed in healthy volunteers in an open label, 4 period, 3-way randomised crossover followed by a non-randomised oral dose using single doses of 20 mg of CBME (10 mg CBD + 10 mg THC). In Periods 1 to 3, the test treatment was administered as a liquid spray according to the randomisation scheme (i.e., sublingually, buccally, oro-pharyngeally). In Period 4 the test treatment was delivered as an oral capsule. There was a six-day washout between each dose.

Primary objectives were to compare the pharmacokinetic profiles of cannabis based medicine extract (CBME) when administered on different areas of the buccal mucosa. Secondary objectives were to investigate the pharmacokinetic profile of CBME when administered as an oral capsule.

Concentrations of THC were higher than the corresponding levels of CBD at most time points. Concentrations of 11-hydroxy-THC exceeded the corresponding concentration of THC at most time points. By 720 min (12 h) post-dose, mean concentrations of each cannabinoid were still above the lower limit of quantification (LLOQ). There was a high degree of inter-subject and intra-subject variability in the plasma concentrations achieved.

T_{max} of CBD and THC occurred earlier following sublingual administration than oro-pharyngeal or buccal although only the difference in T_{max} of CBD compared with buccal was statistically significant. C_{max} of both CBD and THC was greatest following buccal administration although this was not statistically significant. AUC was greatest following oro-pharyngeal and was statistically significantly greater than buccal. The lower bioavailability, as measured by AUC, following buccal administration when compared to the sublingual and oro-pharyngeal routes may be related to the difficulty of spraying onto the inside of the cheek reported during the study and could be due to some loss of spray. Buccal administration of the pump action sublingual spray (PASS) test treatment resulted in a later T_{max} but greater C_{max} when compared to the sublingual and oro-pharyngeal routes. Comparison of the sublingual and oro-pharyngeal routes showed no statistically significant difference in THC or CBD pharmacokinetic parameters other than an earlier T_{max} following sublingual dosing. The oral capsule appeared to show an early T_{max} of both CBD and THC. Mean C_{max} of THC and 11-hydroxy-THC were greater, but in contrast the C_{max} of CBD was lower, than following

the PASS treatments. Relative to THC, the plasma level AUC of 11-hydroxy-THC was proportionally greatest following oral capsules which could be a reflection of greater metabolism by this route. Of the PASS treatments the ratio of 11-hydroxy-THC to THC was greatest following sublingual and least following oro-pharyngeal. There was very wide inter- and to a lesser extent intra-subject variability in pharmacokinetics. Differences in mean values between the routes of administration, even when statistically significant, are small relative to the very wide range of values between subjects. The sublingual and oro-pharyngeal routes of administration appear to have the same pharmacokinetic results. The buccal pharmacokinetic parameters are lower when compared to the sublingual and oro-pharyngeal routes.

A total of 146 adverse events (AEs) occurred in 12 subjects. Two events were classified as moderate (flu-like illness and pharyngeal irritation) and the remaining 144 were classified as mild. All routes of administration were well tolerated by all subjects with no serious AEs and no withdrawals due to AEs.

The overall results indicate that administration of the liquid spray (GW-1000-02) need not be limited to sublingual administration. The oral capsule, has good bioavailability, and provided, as is the case here the formulation is not oil based, may be a viable formulation when self-titration is not necessary.

KEYWORDS. Cannabinoids, cannabis, THC, cannabidiol, medical marijuana, pharmacokinetics, pharmacodynamics, multiple sclerosis, botanical extracts, alternative delivery systems, harm reduction

INTRODUCTION

Cannabis plants (*Cannabis sativa*) contain approximately 60 different cannabinoids (British Medical Association 1997), and in the UK, oral tinctures of cannabis were prescribed until cannabis was made a Schedule 1 controlled substance in the Misuse of Drugs Act in 1971. The prevalence of recreational cannabis use increased markedly in the UK after 1960, reaching a peak in the late 1970s. This resulted in a large number of individuals with a range of intractable medical disorders being exposed to the drug, and many of these discovered that cannabis could apparently relieve symptoms not alleviated by standard treat-

ments. This was strikingly the case with certain neurological disorders, particularly multiple sclerosis (MS). The black market cannabis available to those patients is thought to have contained approximately equal amounts of the cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Baker, Gough, and Taylor 1983). The importance of CBD lies not only in its own inherent therapeutic profile but also in its ability to modulate some of the undesirable effects of THC through both pharmacokinetic and pharmacodynamic mechanisms (McPartland and Russo 2001). MS patients claimed beneficial effects from cannabis in many core symptoms, including pain, urinary disturbance, tremor, spasm and spasticity (British Medical Association 1997). The MS Society estimated in 1998 that up to 4% (3,400) of UK MS sufferers used cannabis medicinally (House of Lords 1998).

Cannabinoid clinical research has often focussed on synthetic analogues of THC, the principal psychoactive cannabinoid, given orally. This has not taken the possible therapeutic contribution of the other cannabinoid and non-cannabinoid plant components into account, or the slow and unpredictable absorption of cannabinoids via the gastrointestinal tract (Agurell et al. 1986). Under these conditions it has been difficult to titrate cannabinoids accurately to a therapeutic effect. Research involving plant-derived material has often reported only the THC content (Maykut 1985) of the preparations, making valid comparisons between studies difficult. GW Pharma Ltd (GW) has developed cannabis based medicine extracts (CBMEs) derived from plant cultivars that produce high and reproducible yields of specified cannabinoids. CBMEs contain a defined amount of the specified cannabinoid(s), plus the minor cannabinoids and also terpenes and flavonoids. The specified cannabinoids constitute at least 90% of the total cannabinoid content of the extracts. The minor cannabinoids and other constituents add to the overall therapeutic profile of the CBMEs and may play a role in stabilising the extract (Whittle, Guy, and Robson 2001). Early clinical studies indicated that sublingual dosing with CBME was feasible, well tolerated and convenient for titration. The concept of self-titration was readily understood by patients and worked well in practice. Dosing patterns tended to resemble those seen in the patient controlled analgesia technique used in post-operative pain control; with small doses administered as and when patients require them, up to a maximal rate and daily limit (GW Pharmaceuticals 2002). The Phase 2 experience has supported some of the wide-range of effects reported anecdotally for cannabis. It has also shown that for most patients the therapeutic bene-

fits of CBMEs could be obtained at doses below those that cause marked intoxication (the 'high'). This is consistent with experience in patients receiving opioids for pain relief, where therapeutic use rarely leads to misuse (Porter and Jick 1980; Portenoy 1990). Onset of intoxication may be an indicator of over-titration. However the range of daily dose required is subject to a high inter-individual variability.

SATIVEX (1:1 THC:CBD CBME) was administered as an oromucosal spray, and contains an equal proportion of THC and CBD, similar to the cannabinoid profile of the cannabis thought to be most commonly available on the European black market (Baker, Gough, and Taylor 1983).

SATIVEX was administered as a liquid spray in three different areas of the mouth and 1:1 THC:CBD CBME as an oral capsule. Each formulation contained equal amounts of CBD and THC. GWPK0112 was a Phase I clinical study that aimed to investigate the relative bioavailability of CBME when administered in different areas of the oral mucosa and the absorption and bioavailability of CBME when administered orally. It was also designed to assess safety and tolerability of the test treatments.

Study Preparations

Sublingual, buccal and oro-pharyngeal test treatments (GW-1000-02) consisted of 25 mg cannabidiol (CBD) + 25 mg Δ^9-tetrahydrocannabinol (THC) per ml formulated in ethanol (eth):propylene glycol (PG) (50:50), with peppermint flavouring with a 100 µl actuation volume (total dose 10 mg CBD + 10 mg THC in 4 actuations). An oral capsule contained 2.5 mg CBD + 2.5 mg THC sprayed onto granulated lactose and encapsulated in soft gelatin capsules (total dose of 10 mg CBD + 10 mg THC 4 capsules).

Study Objectives

Primary objectives were to compare the pharmacokinetic profiles of cannabis based medicine extract (CBME) when administered on different areas of the oral mucosa. Secondary objectives were to investigate the pharmacokinetic profile of CBME when administered as an oral capsule and to assess the safety and tolerability of CBME when administered via different areas of the oral mucosa and *per oral* (po).

METHODS

The final study protocol, final Informed Consent Form, and Investigator Brochure were reviewed by PPD Development Clinic Independent Ethics Committee. Unconditional approval to conduct the study was granted on January 10, 2002. Protocol Amendment was approved by the Ethics Committee on February 6, 2002.

The planning and conduct of this study was subject to national laws and was in conformity with the current revision of the Declaration of Helsinki (October 2000, Edinburgh, Scotland), and the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

A written version of the Informed Consent Form was sent to the subjects before attending screening. At the screening visit and prior to any screening procedures being carried out, the Informed Consent Form was presented verbally to the subjects. The Informed Consent Form detailed no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects that they might expect and any risks involved in taking part; subjects were advised that they would be free to withdraw from the study at any time for any reason without prejudice to future care. Subjects were allowed sufficient time and the opportunity to question the Principal Investigator, their General Practitioner or other independent parties to decide whether they wanted to participate in the study. Written Informed Consent was then obtained by means of subject signature, signature of the person who presented Informed Consent and, if different, the Principal Investigator. A copy of the signed Informed Consent Form was given to the subject and the original signed form is retained in the study site files.

This study was conducted at PPD Development Clinic, 72 Hospital Close, Evington, Leicester, LE5 4WW. The plasma concentration analysis was carried out at ABS Laboratories Ltd, Wardalls Grove, Avonley Road, London, SE14 5ER. The Sponsor for this study was GW Pharma Ltd, Alexander House, Forehill, Ely, Cambridgeshire CB7 4ZA. The test treatments used in this study were formulated by G-Pharm Ltd.

Overall Study Design and Plan–Description

The study was an open label, 4 period, 3-way randomised crossover followed by a non-randomised *po* dose using single doses of 20 mg of CBME (10 mg CBD + 10 mg THC). In Periods 1 to 3 the test treatment was administered to subjects as a liquid spray according to the pre-determined randomisation scheme sublingually (Treatment A), buccally

(Treatment B: inside of cheek), oro-pharyngeally (Treatment C: sprayed generally in mouth), and in Period 4, as an oral capsule (Treatment D). Treatments A, B and C were administered as four actuations (sprays) each five minutes apart. The oral capsule was administered *po* as four capsules each five minutes apart. There was a minimum of six days washout between each. The liquid sprays (GW-1000-02) were formulated in 50% ethanol:50% propylene glycol (PG) at a concentration of 25 mg CBD + 25 mg THC/ml, with peppermint flavouring. The 1:1 THC:CBD capsules were produced as 2.5 mg CBD + 2.5 mg THC sprayed onto granulated lactose in soft gelatin capsules.

Twelve healthy subjects (six male and six female) who complied with all the inclusion and exclusion criteria were required to complete the study in its entirety.

Discussion of Study Design

The present route of administration of CBME used to date in patient studies has been limited to sublingual sprays. Due to the limitation of using a small area of the oral cavity there is at least a potential for mucosal tenderness, lesions or other adverse reactions when used chronically. Therefore the different oral mucosal routes of administration were chosen to assess the plasma concentration-time profiles and pharmacokinetic parameters in relation to the sublingual route.

The oral capsule was chosen to make a preliminary assessment of the plasma concentration-time profiles and pharmacokinetic parameters following oral administration. The dose of CBME administered in this study (10 mg CBD + 10 mg THC) was chosen as this is representative of the dosage of the test treatment when used by patients in a self-titrated regime. It is also known to be well tolerated by subjects and produce quantifiable concentrations of cannabinoids in plasma.

GW specified that only subjects with previous experience with the effects of cannabis be included in their Phase I trials to ensure that subjects recognise the effects they may experience as a result of the CBME given. A crossover design was chosen to enable both inter- and intra-subject comparisons of pharmacokinetic data. The study design was open label as blinding was not possible with different routes of administration. A six-day washout ensured all cannabinoids were below the limit of quantification and assisted in the scheduling of the study in the clinical unit.

Inclusion Criteria

For inclusion in the study subjects were required to fulfil all of the following criteria to ensure they were normal healthy subjects and agreed to participate as per the protocol:

i. Healthy and aged between 18 and 50 years
ii. Had a body mass index (BMI) between 19 and 30 kg/m^2
ii. Had given written informed consent
iv. Had experienced the effects of cannabis more than once
v. Agreed to comply with all the study requirements and restrictions
vi. Agreed to use barrier methods of contraception throughout the study and for 3 months post-dose

Subject demographics and habits are noted in Table 1 and 2.

Exclusion Criteria

To ensure they were normal and healthy, subjects were deemed not acceptable for participation in the study if any of the following criteria applied:

i. Had any cardiovascular, haematological, hepatic, gastro-intestinal, renal, pulmonary, neurological or psychiatric disease which in the opinion of the Investigator was significant
ii. Had a history or presence of schizophrenic-type illness
iii. Had a history of drug or alcohol abuse in the past 12 months
iv. Had a history of allergy to cannabis and/or its metabolites
v. Had used cannabis in any form in the 30 days prior to dosing
vi. Had an abnormal blood or urinalysis result at screening which in the opinion of the Investigator was clinically significant
vii. Had a positive drug screen result (including cannabis) at screening
viii. Had a resting blood pressure > 150/95 or < 90/50 mmHg and a pulse < 40 or > 120 b.p.m.
ix. Had taken a course of prescribed medication (with the exception of oral or depot contraceptives) in the 4 weeks prior to dosing
x. Had taken any over-the-counter or prescription medication (with the exception of oral or depot contraceptives) in the 14 days prior to dosing. If currently taking vitamins or paracetamol subjects were asked to discontinue use at screening

xi. Had been hospitalised in the 3 months prior to dosing
xii. Had lost or donated > 400 ml of blood in the 3 months prior to dosing
xiii. Smoked ≥ 5 cigarettes or used ≥ 1/4 ounces of tobacco per day
xiv. Had participated in a clinical trial in the 3 months prior to dosing
xv. Regularly consumed = 28 (males) or = 21 (females) units of alcohol per week
xvi. Was pregnant or lactating at the time of screening
xvii. Planned to become pregnant during or for three months after completion of the study

Study Restrictions

Subjects were required to abstain from the following for the duration of the study:

i. All foods and beverages containing caffeine and alcohol for 24h pre-each dose until the end of each confinement period
ii. Taking any drugs, including drugs of abuse, prescribed and/or over-the-counter medications for the duration of the study
iii. Smoking/using cigarettes/tobacco products during each confinement period
iv. Donating blood or participating in another clinical study in the 3 months after completion of the study

Removal of Subjects from Therapy or Assessment

The subjects were free to withdraw from the study without explanation at any time and without prejudice to future medical care. Subjects may have been withdrawn from the study at any time if it was considered to be in the best interest of the subject's safety.

TABLE 1. Demographic Data

Statistic	*Age (years)*	*Height (m)*	*Weight (kg)*	*BMI (kg/m²)*
Mean	36.5	1.721	72.38	24.33
Median	36.5	1.73	71.55	24.3
SD	8.38	0.0902	10.785	1.80
Minimum	21	1.58	57.9	21.8
Maximum	48	1.89	98.3	27.5

TABLE 2. Demographics and Habits

Variable	Frequency
Sex:	
Male	6
Female	6
Race:	
Caucasian	11
Mixed Race	1
Smoking:	
None	6
≥ 5 cigarettes/day	6
Alcohol:	
None	0
< 14 units/week	10
< 21 units/week	2
Previous cannabis use: Effects experienced more than once	
Yes	12
No	0

Variable	Frequency
Drugs of Abuse:	
Negative	12
Positive	0
Pregnancy Test:	
Negative	6
Not Required	0
Contraception:	
Yes	12
No	0
CS Blood/Urine Result:	
Yes	0
No	12

CS = clinically significant

TEST TREATMENTS

Treatments Administered

A total single dose of 10 mg CBD + 10 mg THC was administered sublingually, buccally, oro-pharyngeally or *po* to each of 12 subjects on four occasions. Each single dose (10 mg CBD + 10 mg THC) consisted of a series of four actuations of 100 µl (2.5 mg CBD + 2.5 mg THC per actuation) or four capsules (2.5 mg CBD + 2.5 mg THC per capsule) and each actuation/capsule was administered five minutes apart. Every subject received each of the test treatments once. Each vial and capsule blister pack was labelled with no less than subject number, period number, unit number and expiry date.

For the sublingual, buccal and oro-pharyngeal test treatment (Periods 1-3) subjects were randomised to a dose sequence using a Williams Square Design provided by GW. All subjects received the oral capsule in Period 4. All subjects received a single dose of one test treatment in each period.

Selection of Doses in the Study

The dose given has been previously used in GW studies and has been shown to be both well tolerated and produce quantifiable plasma drug concentrations. The dosing regime was chosen as it has been well tolerated by subjects and in general is a reflection of the dosing regimen used in patient studies when the patients are self-titrating.

Selection and Timing of Dose for Each Subject

The test treatments were administered in the morning of each dosing day according to the randomisation scheme. Subjects were dosed in the morning to allow blood samples to be taken and procedures to be carried out up to 12 h post-dose without confining the subjects to the clinical unit overnight. A minimum of six days washout between each dose was specified, as previous data and drug of abuse screens have indicated that concentrations of each cannabinoid from a single dose of CBME are below the limit of quantification by this time. The study was open label.

Subjects were required to abstain from taking any medication, over the counter and prescribed for 14 and 28 days, respectively, prior to dosing until completion of the study unless recommended by their General Practitioner. If any subject took concomitant medications during the restriction period it was noted in the CRF and Investigator judgement as to the subjects continued eligibility was made.

Test Treatment Compliance

Subjects were dosed by the Principal Investigator or suitably trained designee. For the sublingual, buccal and oro-pharyngeal routes subjects were instructed to allow each actuation to absorb and not to swallow if possible. For the *po* route, each capsule was placed on the subject's tongue and they were instructed to swallow the capsule using the glass of water (50 ml) provided to wash each capsule down. Following administration of each capsule the person administering the dose checked the subject's mouth to ensure the capsule had been swallowed. The actual time of administration of each actuation/capsule was recorded in the CRF and the dosing procedure was witnessed by a dose verifier. All subjects received all of the scheduled doses and there were no deviations from dosing target times.

STUDY PROCEDURES

Pre-Study Screening

Subjects were required to undergo a pre-study screen no more than 21 days prior to first dose administration to determine their eligibility to take part in the study. Only those subjects who were healthy and were willing to comply with all the study requirements were deemed eligible for participation. The screening procedures comprised the assessments/measurements shown below.

Demographic Data

The subjects' date of birth, age, sex, race, height, weight, body mass index (BMI), previous cannabis experience, tobacco and alcohol consumption were recorded (Tables 1-2).

Concomitant Medications and Medical History

Subjects were asked to provide details of any drugs, vitamins or medications they had taken in the four weeks prior to screening or were taking at the time of screening. Details of their previous medical history were also recorded. Subjects underwent a physical examination to determine if there were any abnormalities in any body systems. Blood pressure (systolic/diastolic) and pulse were measured after the subject had been seated for no less than two minutes. Oral temperature was also measured. A 12-lead ECG (electrocardiograph) was taken for each subject. At least the following ECG parameters were recorded: HR (heart rate), PR, QT_C and QRS intervals.

Subjects were required to provide a urine sample for routine urinalysis including protein, glucose, ketones, bilirubin, nitrites, blood, urobilinogen, haemoglobin and pH. Microscopy was required to be carried out on any abnormal samples. A pregnancy test was carried out using an HCG Pregnancy Test on all urine samples from female subjects. The samples provided (male and female) were also screened for the drugs of abuse including methadone, benzodiazepines, cocaine, amphetamine, THC, opiates, and barbiturates.

A 4.7 ml blood sample was taken in an ethylenediaminetetraacetic acid (EDTA) blood tube for haematology analysis. A 2.7 ml blood sample was taken in a gel blood tube for routine clinical chemistry analysis.

A blood sample (2.7 ml) was taken in a gel blood tube to screen for the presence of Hepatitis B and/or C.

Pre-Dose Procedures

Subjects were required to arrive at the clinic approximately one hour prior to dosing for each study period. Each subject's health status was updated and pre-dose procedures (health status update, blood pressure and pulse, alcohol and drug of abuse screen and pregnancy test for female subjects) were carried out. Only subjects who complied with the requirements of the study were accepted for inclusion in the study.

Blood Sampling for Plasma CBME Concentration Analysis

Blood samples (4.5 ml) were collected into lithium heparin blood tubes via indwelling cannula or individual venipuncture. Samples were placed immediately into an ice bath until centrifuged (3000 rpm for 10 min at 4°C). The resultant plasma was decanted into two identical pre-labelled silanised amber glass plasma tubes and placed in a freezer at −20°C. Blood samples were collected pre-dose and at 15, 30 and 45 min, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8 and 12 h post start of dose.

Plasma concentrations of CBD, THC and 11-hydroxy-THC were measured in each plasma sample. Urine samples were collected in individual 1 L polypropylene containers. Samples were placed in a refrigerator at + 4°C (range of 0 to 10°C) until the end of each collection period. Samples were then pooled by collection period and the total volume recorded. Sub-samples (2 × 20 ml) were retained (stored frozen at −20°C) for analysis and the remainder of the urine discarded. Urine samples were collected for the following time periods: −1 to 0, 0 to 0.5, 0.5 to 1, 1 to 3, 3 to 6 and 6 to 12 h post-dose. Urine concentrations of 11-COOH THC were measured in each urine sample

Safety Assessments

Each subject was required to provide a urine sample for a urine drug screen at check in for each dosing period. The drug screen was required to be negative for all drugs pre-dose Period 1. For Periods 2 to 4, positive THC results may have occurred due to administration of test treatment in the previous period and therefore screening for THC was not

carried out. The urine sample was required to be negative for all other drugs tested for the subject to be eligible to continue.

Subjects' blood pressure and pulse were measured pre-dose and at 30 min then 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8 and 12 h post start of dosing. A 12-Lead ECG was taken for each subject at the following times: pre-dose and at 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8 and 12 h post-dose.

Adverse Events

Subjects' health was monitored continuously throughout the study for Adverse Events (AEs). All AEs were recorded in the CRF. In addition, subjects' health was monitored by asking non-leading questions pre-dose and at the following times post-dose: 15, 30, 45 min, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 12 h post-dose. All AEs were noted and followed to resolution or at the discretion of the Investigator.

Pregnancy Test

A pregnancy test was carried out using an HCG Pregnancy Test for all female subjects on the urine samples provided at check-in for each study period. The test was required to be negative for the subject to continue in the study.

Palatability/Dose Questionnaire

As soon as possible after the dosing was completed, subjects were asked to complete a questionnaire about the palatability and physical sensation of the test treatment experienced during and immediately after dosing.

Food and Beverages

On study dosing days, subjects were required to abstain from consuming food and beverages for 15 min before the first actuation and 15 min post last actuation (Periods 1-3 only). For Period 4 (capsule dosing) the subjects were not allowed to consume food and beverages for 15 min before dosing and were only allowed to drink the 4 × 50 ml glasses of water provided for dosing until 15 min after dosing was completed.

Lunch and dinner were provided for the subjects at approximately 4 h and 10 h post-dose, respectively. Snacks, e.g., digestive biscuits, were provided *ad libitum* throughout each confinement period as required.

Subjects were required to drink 100 ml of tap water hourly (with the exception of the food and beverage restriction period) from 1 h pre-dose to 10 h post-dose. Decaffeinated beverages were provided *ad libitum* throughout each confinement period as required.

Check-Out Procedures

After completion of the 12 h study procedures at the end of Periods 1, 2 and 3, and if deemed well enough to leave, subjects were discharged from the clinical unit. Prior to discharge, ongoing AEs were updated and follow up arranged if required. Prior to Period 4 discharge, subjects were required to undergo a physical examination, blood samples were taken for haematology and clinical chemistry analyses and a urine sample taken for urinalysis. In addition a 12-lead ECG was taken and vital signs recorded as per screening. Ongoing AEs were updated and if required arrangements were made to follow up with the subjects after they left the clinical unit.

DATA QUALITY ASSURANCE

Study Monitoring

All details regarding the study were documented within individual Case Report Forms (CRFs) provided by GW for each subject. All data recorded during the study were checked against source data and for compliance with GCP (Good Clinical Practice), internal SOPs (Standard Operating Procedures), working practices and protocol requirements. Monitoring of the study progress and conduct was ongoing throughout the study. Monitoring was conducted by GW Clinical Department staff and was conducted according to GW SOPs. Haematology and clinical chemistry analyses were carried out by Leicester General Hospital.

Investigator Responsibilities

The Investigator was responsible for monitoring the study conduct to ensure that the rights of the subject were protected, the reported study

data was accurate, complete and verifiable and that the conduct of the study was in compliance with ICH GCP.

At the end of the study the Principal Investigator reviewed and signed each CRF declaring the data to be true and accurate. If corrections were made after review the Investigator acknowledged the changes by re-signing and dating the CRF.

Clinical Data Management

Data were double entered into approved data tables in Microsoft® Excel 2000 software. Manual checks for missing data and inconsistencies were carried out according to GW's document Data Handling Manual: Manual Checks and queries were raised for any resulting issues. Once the data were clean, i.e., no outstanding queries, then QC checks of 100% of the data for a 10% sample of the patients were conducted in order to make a decision on the acceptability of the data. Any errors were resolved and any error trends across all patients were also corrected. Clinical Quality Audits were carried out.

STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

Statistical and Analytical Plans

With the exception of a SAP being produced prior to carrying out statistical analyses, the statistical analyses were carried out in accordance with the protocol.

Significance Testing and Estimation

The primary analysis was estimation of the pharmacokinetic parameters and thus 95% confidence intervals (CI), in line with current guidelines, are provided for each contrast. Hypothesis testing was secondary in this study. All tests were two-sided.

Pharmacokinetic Analysis

No more than one blood sample per period was omitted for any subject therefore all subjects were considered to be evaluable for pharmacokinetic analysis and were included in the final dataset. All analyses

and summary statistics were carried out and derived using SAS v8. A summary of the mean plasma concentration data is contained in Table 3. Mean pharmacokinetic parameters are contained in Table 4.

Individual plasma concentration-time data and mean profile (mean and standard deviation (SD)) for THC, 11-hydroxy-THC and CBD for each subject were recorded. Plasma concentration-time data were summarised by test treatment group at each time point. Descriptive statistics (number (N), mean, SD, geometric mean, minimum and maximum) were formulated by test treatment for the raw values. Descriptive statistics were calculated for the raw values (N, arithmetic mean, SD, co-efficient of variation (CV%)) and also for the log transformed data (geometric mean, mean of logs and SD of logs).

The pharmacokinetic parameters area under the curve from zero to

TABLE 3. Mean Plasma Concentration Data

Time (min)	*CBD*				*THC*				*11-Hydroxy THC*			
	SL	*Buccal*	*o.p.*	*p.o.*	*SL*	*Buccal*	*o.p.*	*p.o.*	*SL*	*Buccal*	*o.p.*	*p.o.*
0	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
15	0.06	0.04	0.00	0.06	0.05	0.04	0.01	0.08	0.03	0.02	0.00	0.04
30	0.82	0.26	0.24	1.13	1.17	0.47	0.42	2.94	1.12	0.46	0.38	2.59
45	1.00	0.54	1.18	1.61	1.97	1.21	2.68	4.97	2.71	1.60	1.77	5.82
60	1.30	1.18	1.35	1.44	2.83	2.52	3.20	4.29	4.01	2.71	2.92	6.19
75	1.55	1.20	1.80	1.64	3.41	2.74	4.17	4.23	4.93	3.25	4.02	6.75
90	1.60	1.01	1.76	1.61	3.42	2.47	3.98	3.94	5.34	3.43	4.78	6.50
105	1.73	0.99	1.73	1.41	3.56	2.45	3.71	3.09	5.32	3.78	4.65	5.78
120	1.79	1.03	1.56	1.20	3.92	2.69	3.39	2.57	5.35	3.88	4.36	5.13
135	1.53	1.04	1.57	1.25	3.32	2.57	3.30	2.34	4.71	3.70	4.27	4.71
150	1.36	1.06	1.39	1.07	2.87	2.64	2.96	2.04	4.65	4.00	4.01	4.18
165	1.26	1.08	1.34	1.09	2.48	2.63	2.78	2.02	4.56	4.15	3.90	3.71
180	1.23	1.01	1.31	0.97	2.59	2.34	2.69	1.80	4.55	4.05	3.90	3.59
210	0.96	0.96	0.96	0.66	1.80	2.00	1.98	1.17	3.81	3.37	3.20	2.69
240	0.72	1.34	0.78	0.52	1.27	2.36	1.79	0.88	3.03	3.23	2.97	2.30
270	0.67	1.28	1.02	0.57	1.47	2.04	2.31	0.79	2.81	3.10	3.54	1.91
300	0.55	0.73	0.93	0.35	1.15	1.17	2.01	0.56	2.38	2.32	3.11	1.54
330	0.38	0.50	0.71	0.25	0.79	0.82	1.41	0.39	1.76	1.82	2.40	1.23
360	0.33	0.37	0.51	0.21	0.72	0.64	1.02	0.31	1.62	1.45	2.02	1.08
480	0.22	0.22	0.26	0.13	0.33	0.31	0.40	0.17	0.99	0.88	1.06	0.73
720	0.11	0.11	0.15	0.12	0.13	0.12	0.14	0.13	0.56	0.47	0.56	0.48

SL = sublingual *o.p. = oro-pharyngeal* *p.o. = per oral*
NB. Oral capsule administered in Period 4 (except Subject 010)

TABLE 4. Mean Pharmacokinetic Parameters

Treatment	*T_{max} (min)*	*C_{max} (ng/ml)*	*$t_{1/2}$ (min)*	*$AUC_{0\text{-}t}$ (ng/ml.min)*	*$AUC_{0\text{-}\infty}$ (ng/ml.min)*
	Mean Pharmacokinetic Parameters for CBD				
Sublingual	98	2.50	86.35	408.53	427.33
Buccal	168	3.02	108.39	384.13	407.79
Oro-Pharyngeal	123	2.61	105.50	469.08	496.98
per oral	76	2.47	65.41	345.68	362.04
	Mean Pharmacokinetic Parameters for THC				
Sublingual	98	5.54	105.70	808.78	837.25
Buccal	144	6.14	80.47	751.23	770.62
Oro-Pharyngeal	134	6.11	81.20	962.68	985.12
per oral	63	6.35	71.71	705.38	724.79
	Mean Pharmacokinetic Parameters for 11-Hydroxy-THC				
Sublingual	95	6.24	128.84	1522.09	1632.46
Buccal	144	6.13	114.34	1293.14	1362.12
Oro-Pharyngeal	144	6.45	125.78	1477.82	1580.33
per oral	81	7.87	100.10	1410.99	1480.39

NB. Oral capsule administered in Period 4 (except Subject 010)

infinity ($AUC_{0\text{-}\infty}$), area under the curve from zero to t ($AUC_{0\text{-}t}$) and maximum concentration (C_{max}) were log transformed prior to analysis and analysed using the first three periods only. The analysis of variance (ANOVA) model included terms for subject, period and treatment. Least squares means for the treatments were transformed back to the original scale and presented as geometric means. The differences for each of the three pairwise contrasts were exponentiated to express them as ratios of geometric means with 95% confidence intervals.

Time to maximum concentration (T_{max}) and half-life ($t_{1/2}$) were analysed and transformed using the same model as above. The elimination rate constant (K_{el}) is presented descriptively only. Oral capsule data are presented descriptively.

No statistical comparisons were carried out on the urine data.

SAFETY ANALYSIS

Adverse Events

All Adverse Events were coded by Medical Dictionary of Regulatory Activities (MedDRA) and presented by System Organ Class (SOC) and

Preferred Term (PT). For each table, the distribution (n and %) of subjects are presented. The following summary tables were produced: overview summary of treatment-related Adverse Events and all causality Adverse Events.

Clinical Laboratory Tests

For each of the haematology and clinical chemistry parameters, descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised by treatment group at screening and post-study. In addition, descriptive statistics were calculated and summarised for the change from screening.

Listings of clinical chemistry parameters at screening and post-study are presented in Table 5. Abnormal values were designated as H (high) or L (low) in the individual data listings based on the Normal Labora-

TABLE 5. Mean Clinical Chemistry Data

Variable	*Mean pre-study (SD)* *n = 12*	*Mean post-study (SD)* *n = 12*	*Difference (SD)* *n = 12*
AST (iu/l)	20.4 (4.60)	16.2 (3.41)	−4.3 (3.14)
ALT (iu/l)	17.4 (7.91)	15.2 (7.17)	−2.3 (2.34)
Alk phosph. (iu/l)	66.4 (14.64)	61.7 (20.11)	−4.8 (15.26)
GGT (iu/l)	19.2 (6.71)	14.5 (4.70)	−4.7 (3.55)
Total Bilirubin (μmol/l)	11.4 (5.52)	6.0 (2.86)	−5.4 (4.19)
Albumin (g/l)	44.7 (2.77)	38.9 (2.27)	−5.8 (3.93)
Total Protein (g/l)	71.0 (5.06)	63.9 (3.92)	−7.1 (5.12)
Urea (mmol/l)	4.78 (1.011)	4.55 (0.922)	−0.23 (0.916)
Creatinine (μmol/l)	79.3 (10.01)	87.8 (10.08)	8.4 (7.63)
Adjusted Calcium (mmol/l)	2.247 (0.0785)	2.351 (0.1435)	0.104 (0.0914)
Sodium (mmol/l)	137.8 (1.19)	138.3 (1.22)	0.4 (1.24)
Potassium (mmol/l)	4.08 (0.299)	4.11 (0.178)	0.03 (0.281)

tory Reference Ranges. Shift tables were constructed to determine the categorical shifts from screening to post-study. For vital signs and/or blood pressure and pulse descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose.

For each of the ECG parameters (heart rate, PR interval, QT_c interval and QRS width), descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose.

No concomitant medications were taken by any subjects throughout the study. No formal sample size calculation was carried out for this study. Only one minor change to the planned analyses occurred; the planned CI for statistical analyses (90%) was changed to 95%.

Study Subjects

Six healthy male and six healthy female subjects were required to complete the study in its entirety (see demographic data). Six male and six female subjects were randomised and all of those subjects completed the study. No subjects withdrew from the study and no replacements were required.

Protocol Deviations

The following protocol deviations which occurred during the study required investigator judgement:

1. A 4.7 ml blood sample was taken in a gel blood tube blood from each subject at pre-study screening to screen for the presence of Hepatitis B and/or C. The blood sampling for this analysis and results were retained with the individual subject CRFs.
2. Subject 010 was ill for dosing Period 3, however, did wish to continue in the study and a decision was made to delay the subject by one week. The dose to be received in Period 4 would have expired prior to the dosing date therefore the doses for Period 3 and 4 were reversed so that the subject received the oral capsule in Period 3. The actual dates of dosing for each period were recorded in the CRF.

3. A SAP was not produced prior to the statistical analyses being carried out. Statistical analyses were carried as detailed in this report.

The protocol deviations noted are not considered to affect the integrity of the study.

Plasma and Urine Concentration and Plasma Pharmacokinetic Evaluation

All twelve subjects (001 to 012) who were randomised in the study were included in the data analysis. All subjects included in the study complied with all demographic and baseline requirements for inclusion.

Measurements of Compliance

Each test treatment was administered by suitably trained study site clinical staff. No deviations to the dosing regimen were noted for any subject through out the study. The site clinical staff reported a slight difficulty in aiming the buccal dose onto the inside of the cheek, however, each dose was administered with no deviations.

INDIVIDUAL PLASMA CONCENTRATION DATA AND PHARMACOKINETIC RESULTS

Analysis of Plasma Concentration Data

Plasma samples were analysed for CBD, THC and 11-hydroxy-THC according to the analytical protocol. Plasma concentration results were produced in tabular form and concentration-time graphs were produced from these data. The LLOQ for this study was 0.1 ng/ml. Data below the LLOQ are presented as < 0.1 and the actual value measured is presented in parentheses. The actual values measured were used when creating graphs.

The mean values listed in Table 3 show that CBD, THC and 11-hydroxy-THC were all detectable in plasma at around 15-30 min after dosing. Plasma concentrations generally increased to a peak between 45 and 120 min, although following buccal dosing the mean peak of CBD was later, and thereafter diminished though low concentrations were still detectable 720 min after dosing.

Plasma levels of THC (Figure 1) exceeded the corresponding level of

CBD (Figure 2) at almost all time points by a factor of approximately 2 except early and late in the sampling schedule when concentrations of both were low. Approximately 60 min after dosing plasma levels of THC were exceeded by the levels of 11-hydroxy-THC, its principal metabolite, except following oro-pharyngeal dosing when this was delayed and did not occur until after 90 min (Figure 3).

The SDs for the mean plasma concentrations of each cannabinoid, indicate a relatively high inter-subject variability in the rate and extent of absorption (Figures 4-16). This inter-subject variation in the extent of absorption does not seem to be consistently predictable from one treatment to another due to additional intra-subject variability.

Analysis of Urine Concentration Data

Urine samples were analysed for 11-COOH THC according to the analytical protocol. Mean urine concentrations are listed in Table 6 and summarised graphically in Figure 17. The LLOQ (lower limit of quantification) for this study was 0.5 ng/ml. Data below the LLOQ are presented as < 0.5 and the actual value measured is presented in parentheses. Urine samples were collected in polypropylene containers and the binding of cannabinoids to this material is unknown. Therefore the

FIGURE 1. GWPK0112 Mean CBME THC PK Data Following Administration of CBME via Different Routes

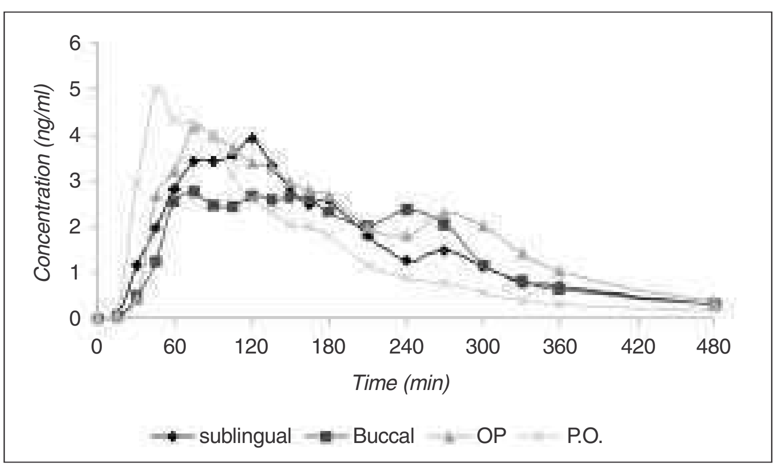


FIGURE 2. GWPK0112 Mean CBME CBD PK Data Following Administration of CBME via Different Routes

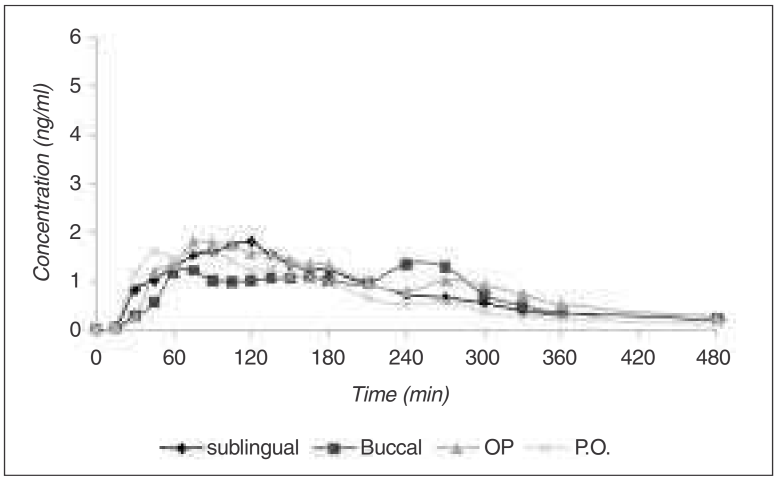


FIGURE 3. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following Administration of CBME via Different Routes

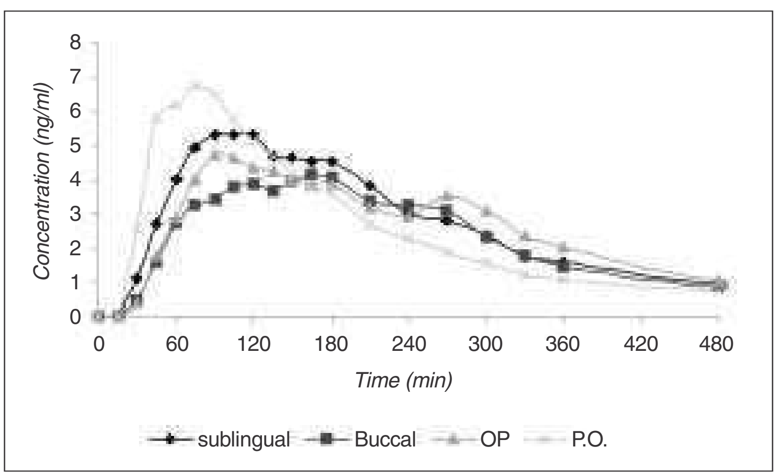


FIGURE 4. GWPK0112 Mean CBME THC PK Data Following Sublingual Administration

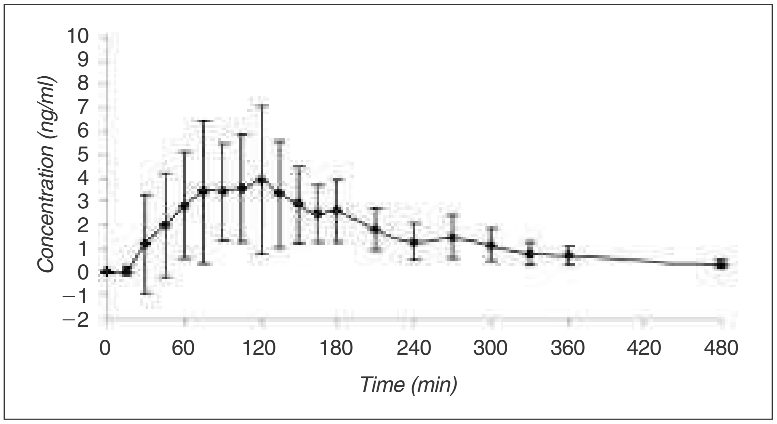
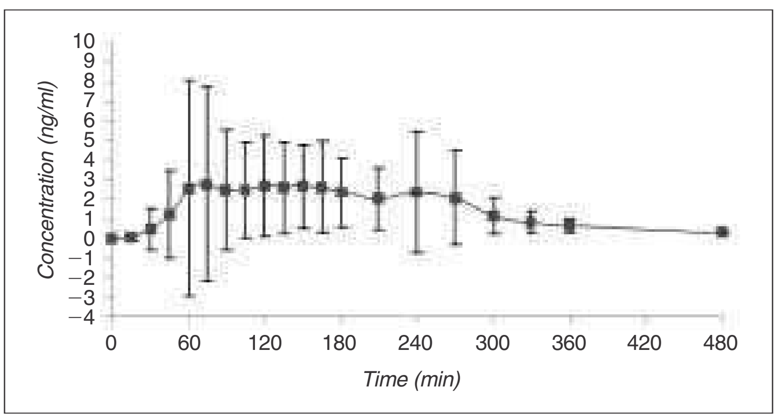


FIGURE 5. GWPK0112 Mean CBME THC PK Data Following Buccal Administration



reliability of the data is not known. Pre-dose, some subjects had quantifiable amounts of 11-COOH THC in urine. Mean pre-dose concentrations were: 0.21, 0.27, 0.36 and 0.91 ng/ml in the urine samples collected in the hour prior to sublingual, buccal, oro-pharyngeal or oral capsule dosing, respectively.

FIGURE 6. GWPK0112 Mean CBME THC PK Data Following Oro-Pharyngeal Administration

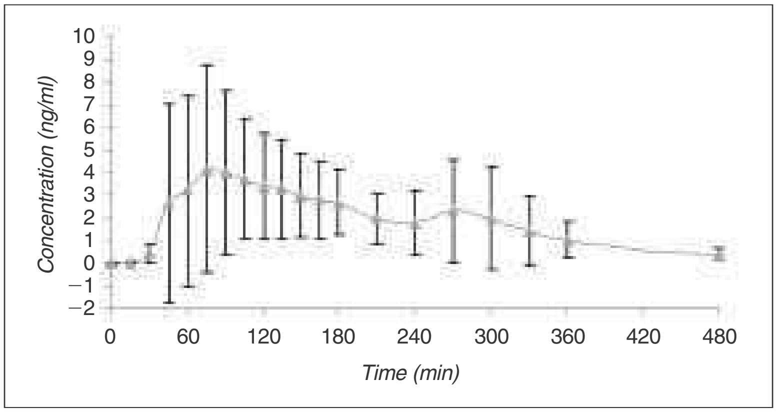
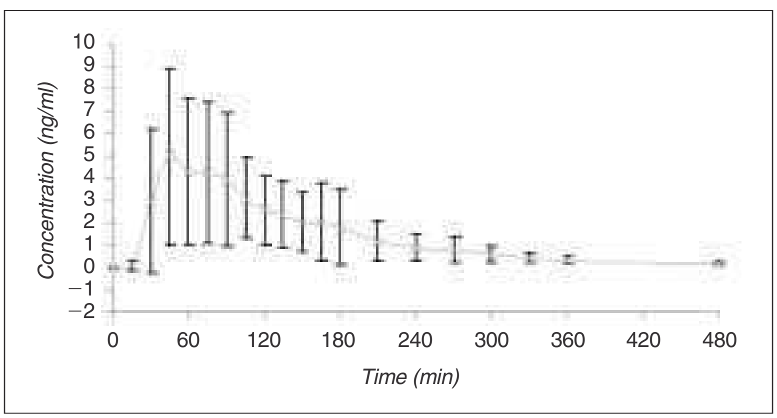


FIGURE 7. GWPK0112 Mean CBME THC PK Data Following P.O. Administration (Capsule)



No unchanged CBD or THC were detected in urine following administration of each test treatment. A metabolite of THC (11-COOH THC) was detected and was quantified. Following each treatment the excretion of 11-COOH THC was low up to one hour after dosing, increased markedly during the 1-3 h post-dose period and increased further during

FIGURE 8. GWPK0112 Mean CBME Plasma Concentration Results Following Sublingual Administration (Subjects 1-12)

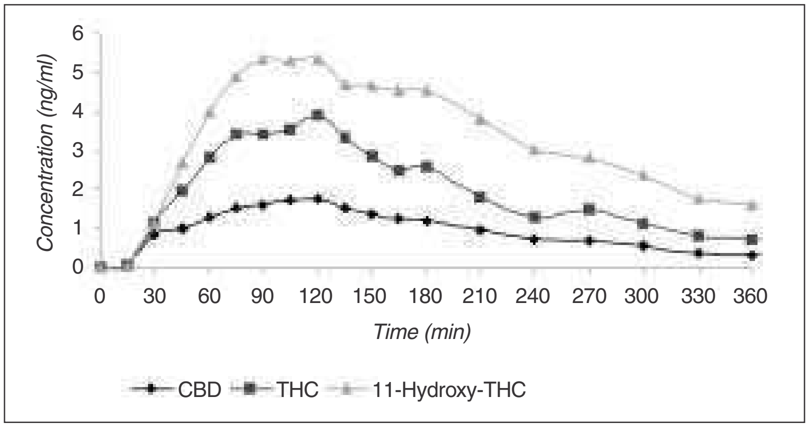
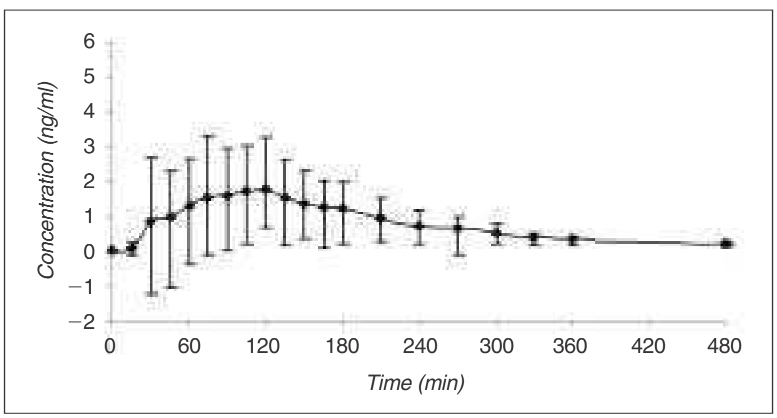


FIGURE 9. GWPK0112 Mean CBME CBD PK Data Following Sublingual Administration



the 3-6 h period before declining again during the 6-12 h post-dose period (Table 6). All four test treatments showed a similar pattern. The highest total mean excretion apparently was achieved following administration of the oral capsule followed by the sublingual spray, buccal spray and finally oro-pharyngeal spray. However, as excretion of 11-hydroxy-THC was apparently not complete after the 6-12 h collection period, these findings should be interpreted with caution.

FIGURE 10. GWPK0112 Mean CBME CBD PK Data Following Buccal Administration

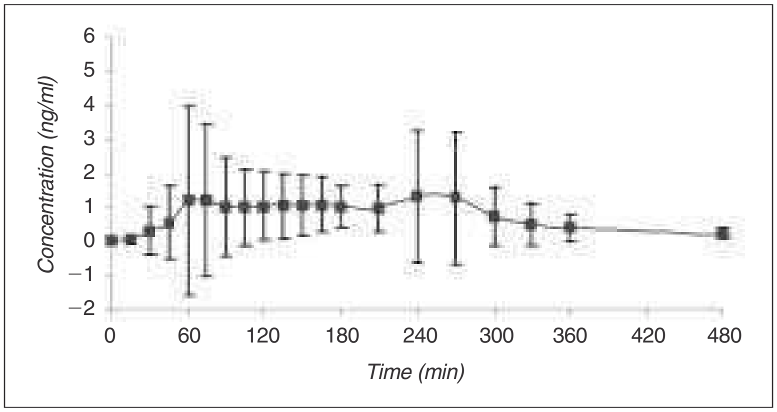
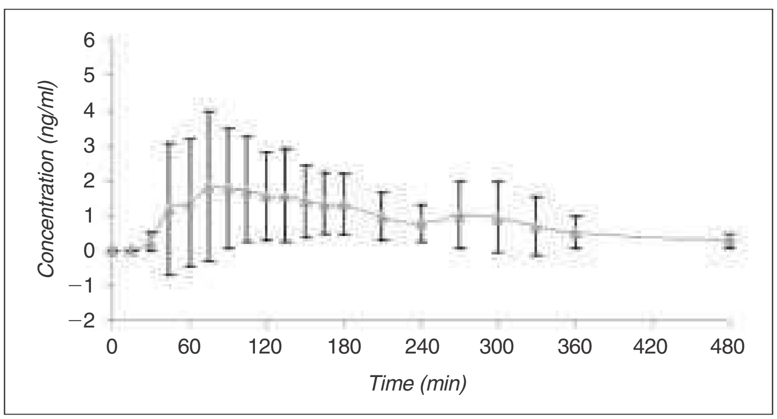


FIGURE 11. GWPK0112 Mean CBME CBD PK Data Following Oro-Pharyngeal Administration



Analysis of Pharmacokinetic Parameters

Pharmacokinetic parameters were calculated using WinNonlin® Professional 3.1. The model used was a non-compartmental, linear trapezoidal analysis. Values below the LLOQ are not considered reliable and therefore were not used when calculating PK parameters. Mean pharmacokinetic values are presented in Table 4 and displayed in the graphs.

FIGURE 12. GWPK0112 Mean CBME CBD PK Data Following P.O. Administration (Capsule)

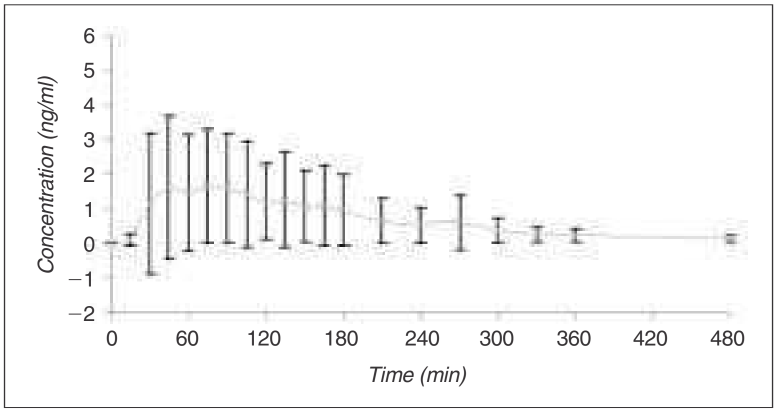
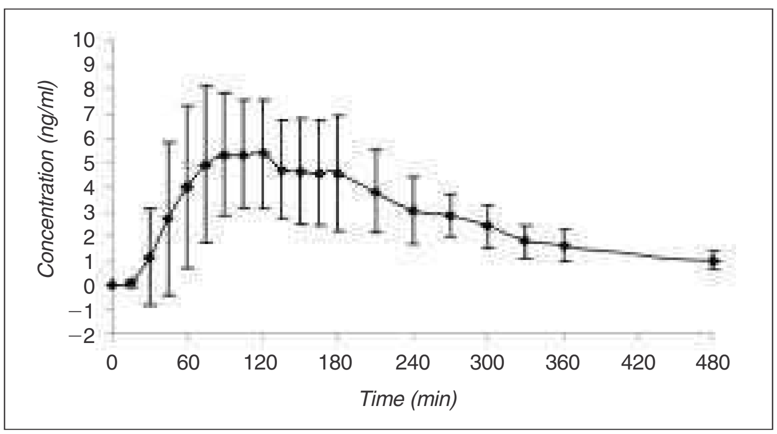


FIGURE 13. GWPK0112 Mean CBME 11-Hydroxy THC PK Data Following Sublingual Administration



Analysis of PASS Sublingual, Buccal and Oro-Pharyngeal Pharmacokinetic Parameters

Mean T_{max} of both THC (Table 7) and CBD (Table 8) occurred earlier following sublingual administration (98 min) than oro-pharyngeal (123 min CBD, 134 min THC) (Tables 9 and 10) or buccal (168 min

FIGURE 14. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following Buccal Administration

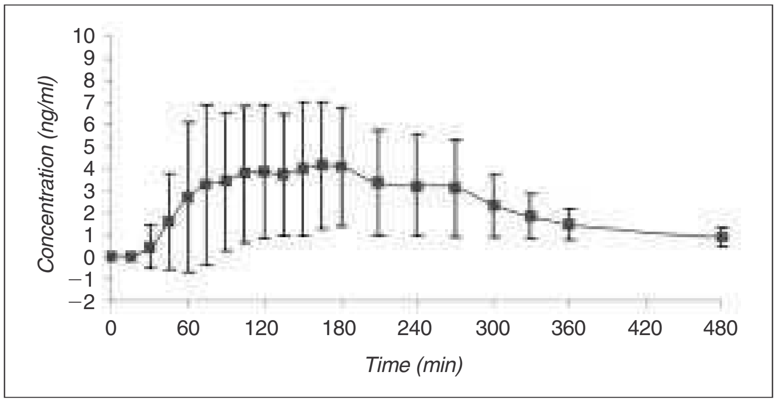
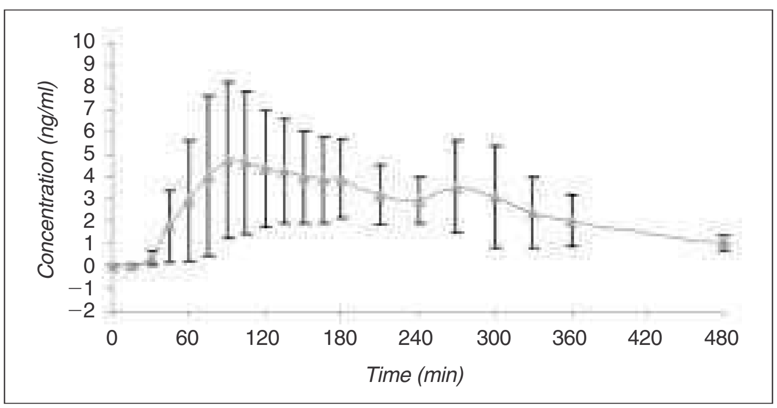


FIGURE 15. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following Oro-Pharyngeal Administration



CBD, 144 min THC) (Tables 11 and 12) though only the difference in CBD T_{max} between buccal and sublingual administration reached statistical significance ($p = 0.0059$). C_{max} of both THC and CBD was greatest following buccal administration then oro-pharyngeal and finally sublingual, although none of the differences reached statistical significance. $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of both THC and CBD were greatest following oro-pharyngeal administration followed by sublingual then

FIGURE 16. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following P.O. Administration (Capsule)

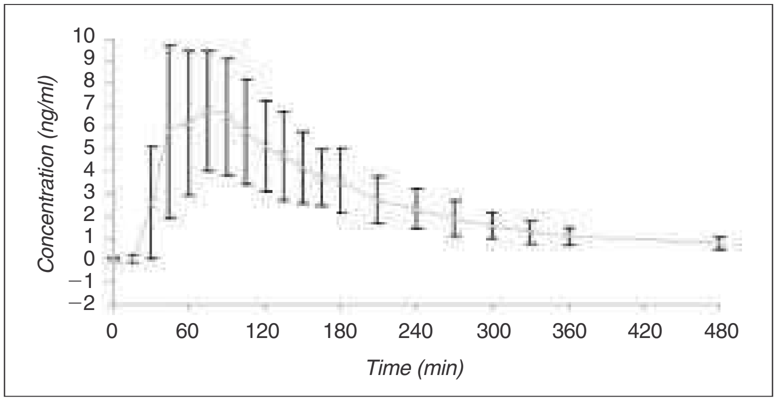


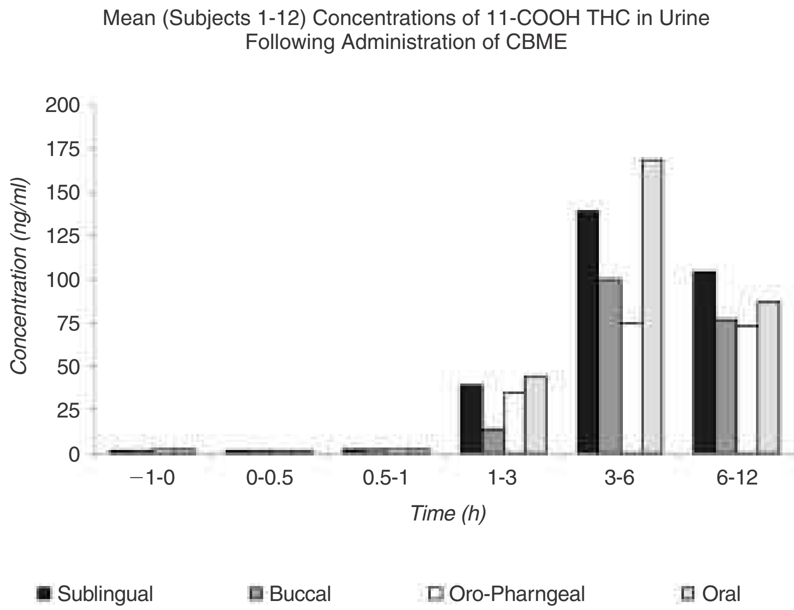
TABLE 6. Mean Excretion of 11-COOH THC in Urine (ng/ml) per Time Period

Time Period (h)	Test Treatment			
	Sublingual	Buccal	Oro-Pharyngeal	Oral Capsule
−1-0	0.21	0.27	0.36	0.91
0-0.5	0.05	0.20	0.32	0.29
0.5-1	1.10	0.75	0.89	1.61
1-3	38.45	13.55	34.53	44.17
3-6	139.33	99.29	74.40	168.84
6-12	104.08	75.97	73.30	87.12
Total	283.22	190.03	183.8	302.94

buccal dosing. The differences in $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of THC between oro-pharyngeal and buccal dosing were statistically significant ($AUC_{0\text{-}t}$ $p = 0.0024$ and $AUC_{0\text{-}\infty}$ $p = 0.0018$). The bioavailability of THC was approximately twice that of CBD irrespective of the site of application.

There were significant differences in the pharmacokinetic parameters of 11-hydroxy-THC between the different administrations. T_{max} of 11-hydroxy-THC occurred statistically significantly earlier (95 min) after sublingual dosing (Table 13) than buccal (144 min, $p = 0.038$) (Table 14) or oro-pharyngeal (144 min, $p = 0.038$) (Table 15). There were no statistically significant differences in C_{max} of 11-hydroxy-THC between treatments. $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were significantly lower after

FIGURE 17. Mean Urine 11-COOH THC Concentrations (ng/ml) in Urine Following Administration of Each Test Treatment



NB. Mean data taken from Table 3

TABLE 7. Summary of Plasma THC Pharmacokinetic Parameters–PASS Sublingual

Statistic	*$AUC_{0-\infty}$ (ng/ml · min)*	*AUC_{0-t} (ng/ml · min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	837.3	808.8	5.54	97.5	105.7
Geometric mean	772.5	745	4.64	-	-
Minimum	429.3	406.9	1.14	60	45.4
Maximum	1857.5	1812	12.13	180	193.7
SD	387.34	378.36	3.346	35.32	39.743
CV%	46.3	46.8	60.4	36.2	37.6
Log transformed:					
Mean	6.6496	6.6134	1.5349	-	-
SD	0.4049	0.4087	0.651	-	-

TABLE 8. Summary of Plasma CBD Pharmacokinetic Parameters–PASS Sublingual

Statistic	$AUC_{0-\infty}$ (ng/ml ·min)	AUC_{0-t} (ng/ml ·min)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2}$ (min)
N	12	12	12	12	12
Arithmetic mean	427.3	408.5	2.5	97.5	86.35
Geometric mean	370.1	344.3	1.87	-	-
Minimum	137.5	93.8	0.27	45	44.2
Maximum	1106.4	1083.8	6.55	180	201.6
SD	258.86	259.86	1.8281	40.7	47.18
CV%	60.6	63.6	73.2	41.7	54.6
Log transformed:					
Mean	5.9137	5.8414	0.6286	-	-
SD	0.5537	0.625	0.866	-	-

TABLE 9. Summary of Plasma THC Pharmacokinetic Parameters–PASS Oro-Pharyngeal

Statistic	$AUC_{0-\infty}$ (ng/ml ·min)	AUC_{0-t} (ng/ml ·min)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2}$ (min)
N	12	12	12	12	12
Arithmetic mean	985.1	962.7	6.11	133.8	81.2
Geometric mean	897.7	874.2	5.06	-	-
Minimum	413.3	404.4	1.94	45	41.8
Maximum	1772.1	1758.3	15.68	300	162.5
SD	440.27	439.99	3.998	91.23	30.838
CV%	44.7	45.7	65.5	68.2	38
Log transformed:					
Mean	6.7998	6.7733	1.621	-	-
SD	0.4545	0.4618	0.648	-	-

TABLE 10. Summary of Plasma CBD Pharmacokinetic Parameters–PASS Oro-Pharyngeal

Statistic	$AUC_{0-\infty}$ (ng/ml ·min)	AUC_{0-t} (ng/ml ·min)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2}$ (min)
N	12	12	12	12	12
Arithmetic mean	497	469.1	2.61	122.5	105.5
Geometric mean	417.3	387.8	2.01	-	-
Minimum	128.2	109.4	0.41	45	41.4
Maximum	1286.8	1201.3	6.36	300	186.1
SD	319.34	307.78	1.907	67.94	47.879
CV%	64.3	65.6	73	55.5	45.4
Log transformed:					
Mean	6.0337	5.9606	0.7004	-	-
SD	0.6238	0.657	0.7923	-	-

TABLE 11. Summary of Plasma THC Pharmacokinetic Parameters–PASS Buccal

Statistic	*$AUC_{0-\infty}$ (ng/ml·min)*	*AUC_{0-t} (ng/ml·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	770.6	751.2	6.14	143.8	80.47
Geometric mean	664.6	640.4	4.39	-	-
Minimum	233.6	225.3	0.88	60	44.6
Maximum	1666.9	1656	19.78	270	168.4
SD	427.22	431.19	5.367	65.06	38.807
CV%	55.4	57.4	87.4	45.3	48.2
Log transformed:					
Mean	6.4992	6.4621	1.4791	-	-
SD	0.5852	0.6081	0.8827	-	-

TABLE 12. Summary of Plasma CBD Pharmacokinetic Parameters–PASS Buccal

Statistic	*$AUC_{0-\infty}$ (ng/ml·min)*	*AUC_{0-t} (ng/ml·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	407.8	384.1	3.02	167.5	108.39
Geometric mean	328.1	287.9	1.82	-	-
Minimum	100.5	80.4	0.29	60	38.2
Maximum	862.7	852.4	9.91	270	451.4
SD	267.8	277.34	3.1478	78.81	122.936
CV%	65.7	72.2	104.1	47.1	113.4
Log transformed:					
Mean	5.7932	5.6625	0.5996	-	-
SD	0.7146	0.8429	1.0925	-	-

TABLE 13. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–PASS Sublingual

Statistic	*$AUC_{0-\infty}$ (ng/ml·min)*	*AUC_{0-t} (ng/ml·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	1632.5	1522.1	6.24	95	128.84
Geometric mean	1508.2	1410.6	5.7	-	-
Minimum	635.7	621.6	2.67	60	54.3
Maximum	3058.3	2906.3	10.77	165	270.3
SD	687.19	638.68	2.744	26.63	59.252
CV%	42.1	42	43.9	28	46
Log transformed:					
Mean	7.3187	7.2518	1.7409	-	-
SD	0.4198	0.4079	0.45	-	-

TABLE 14. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–PASS Buccal

Statistic	*$AUC_{0-\infty}$ (ng/ml ·min)*	*AUC_{0-t} (ng/ml ·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	1362.1	1293.2	6.13	143.8	114.34
Geometric mean	1191.5	1123.2	5.48	-	-
Minimum	357.1	345.1	1.83	60	66.4
Maximum	3308.9	3152.3	11.25	270	323.5
SD	753.7	728.83	2.878	69.91	74.866
CV%	55.3	56.4	46.9	48.6	65.5
Log transformed:					
Mean	7.083	7.0239	1.7002	-	-
SD	0.5582	0.574	0.524	-	-

TABLE 15. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–PASS Oro-Pharyngeal

Statistic	*$AUC_{0-\infty}$ (ng/ml ·min)*	*AUC_{0-t} (ng/ml ·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	1580.3	1477.8	6.45	143.8	125.78
Geometric mean	1520.1	1420.6	5.94	-	-
Minimum	737	688.7	2.95	75	59
Maximum	2483.7	2379.3	13.49	300	260.8
SD	440.08	420.39	2.905	73.05	56.496
CV%	27.8	28.4	45.1	50.8	44.9
Log transformed:					
Mean	7.3265	7.2588	1.7815	-	-
SD	0.3019	0.3032	0.416	-	-

buccal than either sublingual or oro-pharyngeal dosing. The ratios of AUC_{0-t} of 11-hydroxy-THC to THC were 1.5, 1.7 and 1.9:1 (calculated from Table 4) following oro-pharyngeal, buccal and sublingual dosing, respectively.

Inter-subject variability in pharmacokinetics was considerable with CV% of the order of 45 to 70% in AUC, 38 to 68% in T_{max} and 44 to 113% in C_{max} (calculated from Table 4). Following each treatment differences between the lowest and highest C_{max} values observed in individual subjects ranged from 8 to 46-fold, with the range being generally greater for CBD than THC. The difference between lowest and highest AUC_{0-t} was less, being of the order of 11-fold for CBD after all formulations and 4 to 7-fold for THC. While some individuals tended to show

consistency in high or low AUC or C_{max} values across all treatments, others showed considerable intra-subject variability.

Analysis of Oral Capsule Pharmacokinetic Parameters

Following administration of the oral capsules the mean T_{max} of CBD was 76 min (Table 16) and for THC 63 min (Table 17). The C_{max} of CBD was 2.47 ng/ml and C_{max} of THC was 6.35 ng/ml. T_{max} of CBD, THC and 11-hydroxy-THC (Table 18) occurred earlier following dosing with oral capsules than dosing with sublingual buccal or oro-pharyngeal sprays.

TABLE 16. Summary of Plasma CBD Pharmacokinetic Parameters–Oral Capsule

Statistic	*$AUC_{0-\infty}$ (ng/ml · min)*	*AUC_{0-t} (ng/ml · min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	362	345.7	2.47	76.3	65.41
Geometric mean	259.1	240.8	1.72	-	-
Minimum	79.1	67.3	0.47	30	22.9
Maximum	932.8	921.1	7.55	180	108.5
SD	298.28	296.28	2.233	50.55	27.58
CV%	82.4	85.7	90.3	66.3	42.2
Log transformed:					
Mean	5.5571	5.4838	0.5406	-	-
SD	0.8779	0.9129	0.8964	-	-

TABLE 17. Summary of Plasma THC Pharmacokinetic Parameters–Oral Capsule

Statistic	*$AUC_{0-\infty}$ (ng/ml · min)*	*AUC_{0-t} (ng/ml · min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	724.8	705.4	6.35	62.5	71.72
Geometric mean	656.2	635	5.79	-	-
Minimum	366	357.8	3.04	30	36.8
Maximum	1744.4	1731.8	14.55	165	134.1
SD	375.66	377.07	3.122	38.82	25.583
CV%	51.8	53.5	49.2	62.1	35.7
Log transformed:					
Mean	6.4864	6.4537	1.7564	-	-
SD	0.45	0.4619	0.4327	-	-

TABLE 18. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–Oral Capsule

Statistic	$AUC_{0-\infty}$ (ng/ml · min)	AUC_{0-t} (ng/ml · min)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2}$ (min)
N	12	12	12	12	12
Arithmetic mean	1480.4	1411	7.87	81.3	100.1
Geometric mean	1394.5	1331.6	7.4	-	-
Minimum	623.6	608.9	4.79	45	67.1
Maximum	2470.5	2389.4	13.64	180	132.4
SD	515.87	487.29	2.958	38.09	17.69
CV%	34.8	34.5	37.6	46.9	17.7
Log transformed:					
Mean	7.2403	7.1941	2.0021	-	-
SD	0.3724	0.3655	0.3585	-	-

Mean AUC_{0-t} and $AUC_{0-\infty}$ of CBD (345.68 and 362.04 ng/ml.min, respectively) were lower, whereas the mean AUC_{0-t} and $AUC_{0-\infty}$ of THC (705.38 and 724.79 ng/ml.min, respectively) were greater following dosing with oral capsules than with the sublingual, buccal or oro-pharyngeal sprays. The bioavailability of THC was approximately twice that of CBD. The mean T_{max} of 11-hydroxy-THC (81 min) was a little later than that of CBD or THC, though still earlier than following dosing with sublingual buccal or oro-pharyngeal sprays. The C_{max} (7.87 ng/ml) for 11-hydroxy-THC was greater than that of THC. Mean AUC_{0-t} and $AUC_{0-\infty}$ (1410.99 and 1480.39 ng/ml.min, respectively) were twice the corresponding values for THC.

Analysis of Safety Parameters

For each of the blood pressure and pulse parameters descriptive statistics (n, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose.

For each of the ECG parameters (heart rate, PR interval, QT_c interval and QRS width), descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose. For QT_c, absolute values and changes from pre-dose were categorised as borderline, normal, prolonged according to CPMP guidelines.

Statistical/Analytical Issues

There were no specific statistical or analytical issues in this study.

Plasma Concentration Conclusions

Mean data indicate an almost simultaneous appearance of all three cannabinoids in plasma at 30 minutes after dosing, though in individuals there was considerable variability in the time to first appearance of the cannabinoids (range 15-105 minutes).

Concentrations of THC were higher than the corresponding levels of CBD at most time points. Concentrations of 11-hydroxy-THC exceeded the corresponding concentration of THC at most time points after 45 min. By 720 min (12 h) post-dose, mean concentrations of each cannabinoid were still above the LLOQ.

There was a high degree of inter-subject and intra-subject variability in the plasma concentrations achieved.

Urine Concentration Conclusions

No statistical analyses were carried out on the urine data. Urine samples were collected in polypropylene containers and due to the affinity of cannabinoids to plastic, the accuracy of the urine data is not known. 11-COOH THC (a metabolite of THC) was detected in urine throughout the sampling period in quantifiable amounts.

The excretion of 11-COOH THC began within the first 0.5 to 1 hour after dosing, peaked during the 3-6 h collection period and thereafter decreased. Administration of the oral capsules resulted in resulted in the greatest total concentrations of 11-COOH THC excreted, followed by dosing sublingually and the buccal and oro-pharyngeal routes showed approximately the same extent of excretion of 11-COOH THC throughout the sampling period.

Pharmacokinetic Conclusions

T_{max} of CBD and THC occurred earlier following sublingual administration than oro-pharyngeal or buccal although only the difference in T_{max} of CBD compared with buccal was statistically significant.

C_{max} of both CBD and THC for the PASS test treatments was greatest following buccal administration although this was not statistically significant. AUC was greatest following oro-pharyngeal administration

and was statistically significantly greater than following buccal administration. The lower bioavailability, as measured by AUC, following buccal administration when compared to the sublingual and oro-pharyngeal routes may be related to the difficulty of spraying onto the inside of the cheek reported during the study. Buccal administration of the PASS test treatment resulted in a later T_{max} but greater C_{max} when compared to the sublingual and oro-pharyngeal routes.

Comparison of the sublingual and oro-pharyngeal routes showed no statistically significant difference in THC or CBD pharmacokinetic parameters measured.

Pharmacokinetic parameters following administration of the oral capsule were not statistically compared to the other routes as this was an early investigation into the safety and tolerability of this dose route. However, this dosage form and route of administration appeared to show an early T_{max} of both CBD and THC. Mean C_{max} of THC and 11-hydroxy-THC were greater, but in contrast the C_{max} of CBD was lower, than following the PASS treatments.

Relative to THC, the plasma level AUC of 11-hydroxy-THC was proportionally greatest following dosing with the oral capsules which could be a reflection of greater metabolism by this route. Of the PASS treatments the ratio of 11-hydroxy-THC to THC was greatest following sublingual and least following oro-pharyngeal dosing.

The oral capsule has good bioavailability, and provided, as is the case here, the formulation is not oil based, may be a viable formulation when self-titration is not necessary. There was very wide inter- and to a lesser extent intra-subject variability in pharmacokinetics. Differences in mean values between the routes of administration, even when statistically significant, are small relative to the very wide range of values between subjects.

Safety Evaluation

The test treatments were well tolerated by all subjects with no Serious Adverse Events (SAEs) recorded throughout the study and no subject withdrawals. Peak concentrations of cannabinoids in plasma did not correspond with AEs or other events.

Adverse Events

A summary of treatment-emergent/treatment-related AEs is presented in Table 19. A total of 146 AEs occurred in 12 subjects through-

TABLE 19. Summary of Subjects Who Experienced Treatment Emergent, Treatment Related Adverse Events

Event	*Treatment*			
	A	*B*	*C*	*D*
No. of subjects with ≥ 1 event	12 (100%)	12 (100%)	11 (91.7%)	10 (83.3%)
Cardiac disorders	2	2	1	2
Palpitations	2			
Sinus tachycardia	1	2	1	2
Gastrointestinal disorders	6	6	6	2
Aptyalism				2
Throat irritation	6	6	6	
General disorders and administration site conditions	4	7	6	5
Application site irritation	3	3	4	
Feeling cold		1	1	1
Feeling of relaxation	1	2	1	3
Lethargy	1	1	2	1
Injury, poisoning and procedural complications	2	1	3	2
Drug toxicity NOS	2	1	3	2
Nervous system disorders	9	10	9	9
Coordination abnormal NOS				1
Disturbance in attention	1		1	3
Dizziness	7	5	8	7
Dysgeusia	1	1		
Headache NOS	1	3	1	1
Paraesthesia	2	2		3
Paraesthesia oral NOS	1	3		1
Somnolence	4	3	2	5
Psychiatric disorders	2	2	1	1
Anxiety NEC	1	1		
Dissociation	1	1	1	
Restlessness	1	2	1	1
Skin and subcutaneous tissue disorders	1	0	0	0
Rash maculo-papular	1			

Note: treatment related = definitely, probably, possibly related

out the study. Two events were classified as moderate (flu-like illness and pharyngeal irritation) and the remaining 144 were classified as mild. Three events were classified as not related to test treatment, (flu-like illness, coryza and feels cold), leaving 143 considered to be possibly, probably or definitely related to the test treatment. At the end

of the study, all the events, with the exception of maculo-papular rash of the neck and shoulders, had resolved without treatment. The maculo-papular rash did not require treatment and follow up was continued at the clinical site until resolution.

The most common AEs experienced were dizziness, throat irritation, somnolence, and application site irritation.

The number of subjects experiencing treatment related throat irritation were the same for the sublingual (6), buccal (6) and oro-pharyngeal (6) routes, however there were none reported for the oral capsule. Treatment related application site irritation was experienced with the sublingual (3), buccal (3) and oro-pharyngeal (4), however no application site irritation AEs were reported for the oral capsules. Treatment related paraesthesia was experienced after dosing sublingually (2), buccally (2) and with the oral capsule (3), however no paraesthesia AEs were reported in the subjects receiving PASS oro-pharyngeally.

There were no deaths or SAEs during the study, and no withdrawals due to AEs.

Clinical Laboratory Evaluation

There were no clinically significant changes in the individual or mean haematology or clinical chemistry parameters from pre-dose to post-study (Table 5). There were no haematology or clinical chemistry parameter results (or changes from pre-study to post-study) observed, which were considered to be clinically significant. There were no clinically significant individual subject changes in any safety parameters noted throughout the study. There were no results observed or reported throughout the study that were considered by the investigator to be clinically significant abnormal results.

Vital Signs, Physical Findings and Other Observations Related to Safety

There were no changes in vital signs, physical findings or other safety analyses recorded throughout the study that were considered by the investigator to be clinically significant.

Safety Conclusions

All test treatments were well tolerated by all subjects with no SAEs occurring throughout the study. Most of the AEs experienced by sub-

jects were mild and resolved without treatment. The most common AEs experienced across all test treatments were dizziness, throat irritation, somnolence, and application site irritation. The only notable differences in AEs between test treatment groups were throat irritation and application site irritation, which were not seen with the oral capsule, and paraesthesia which was not seen with oro-pharyngeal dosing.

DISCUSSION AND OVERALL CONCLUSIONS

All routes of administration were well tolerated by all subjects with no SAEs and no withdrawals due to AEs.

There was a wide intra-subject variability in each of the pharmacokinetic parameters. This variation may be due to many factors such as amount of dose swallowed instead of absorption through the oral mucosa, breakfast on the morning of dosing, or levels of exercise undertaken by each subject.

By 720 min (12 h) post-dose mean concentrations of each cannabinoid were still above the LLOQ, indicating that redistribution within the body may still be occurring. The sublingual and oro-pharyngeal routes of administration appear to have the same pharmacokinetic results. The buccal pharmacokinetic parameters are lower when compared to the sublingual and oro-pharyngeal routes. Overall, the results indicate that administration of the liquid spray (GW-1000-02) need not be limited to sublingual administration.

The oral capsule has good bioavailability and provided as is the case here, the formulation is not oil based, may be a viable formulation when self-titration is not necessary. The urine samples were collected in polypropylene containers therefore the reliability of the urine concentration data is not known. Excretion in urine for all four test treatments showed a similar pattern with excretion in significant amounts beginning as the concentrations of THC and 11-hydroxy-THC in plasma were decreasing. This suggests that a portion of the cannabinoids are rapidly metabolised and excreted via the kidneys and are not re-distributed to body tissues such as adipose tissue. In some subjects' excretion of 11-COOH-THC was still occurring pre-next dose suggesting that a portion of the test treatment is re-distributed to body tissues and slowly eliminated via the kidneys. During this slow elimination phase (12 hours to six days), no CBD, THC or 11-hydroxy-THC can be detected in plasma suggesting that after a six day washout period either all THC is metabolised to 11-COOH THC or is re-distributed to other body tissues.

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A Phase I, Double Blind, Three-Way Crossover Study to Assess the Pharmacokinetic Profile of Cannabis Based Medicine Extract (CBME) Administered Sublingually in Variant Cannabinoid Ratios in Normal Healthy Male Volunteers (GWPK0215)

G. W. Guy
P. J. Robson

SUMMARY. Primary objectives of this study were to assess the pharmacokinetic characteristics of CBME when administered sublingually in different ratios, to determine if the pharmacokinetic profiles of THC and its metabolite 11-hydroxy-THC are different when administered sublingually in different formulations, and to characterise the pharmacokinetic profile of CBD when administered with THC in equal amounts.

G. W. Guy and P. J. Robson are affiliated with GW Pharmaceuticals plc, Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, UK.

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Secondary objectives were to determine if there was a correlation between intoxication levels and plasma concentrations of THC and/or its metabolite 11-hydroxy-THC, and to assess safety and tolerability of CBME when administered sublingually.

Methodology employed a double-blind, randomised, three-way crossover study of placebo, High THC and CBD:THC administered sublingually as a liquid spray. Twenty-four subjects were planned, dosed, completed the study and were analysed.

Test products were Δ^9-tetrahydrocannabinol (THC, formulated as 25 mg THC per ml) with or without cannabidiol (CBD) (formulated as 25 mg CBD + 25 mg THC per ml) formulated in ethanol (Eth):propylene glycol (PG) with peppermint (ppmt) flavouring or matching placebo, administered with a 100 µl pump. Each subject received one single dose of 10 mg THC and one single dose of 10 mg CBD + 10 mg THC plus a single dose of placebo in a randomised manner on three separate occasions. The washout period was six days between each dose. Placebo was Eth:PG in a 50:50 ratio with ppmt flavouring, administered with a 100 µl actuator pump.

Mean plasma concentrations show that following administration of both High THC and CBD:THC formulations CBD and or THC was detectable in plasma in measurable concentrations 15-30 minutes after dosing, although individual subjects showed quite wide variability, 15 to 135 minutes, to appearance measurable concentrations. At all time points up to 180 minutes after dosing mean concentrations of THC were greater following the High THC formulation than CBD:THC. Concentrations of THC were also greater than corresponding concentrations of CBD following the CBD:THC treatment.

There were no statistically significant differences in mean C_{max}, $t_{1/2}$, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of both THC and 11-hydroxy-THC between the High THC and CBD:THC formulations. THC T_{max} was statistically significantly later following CBD:THC than High THC ($p = 0.014$) and this was the only statistically significant difference in pharmacokinetic parameters between the treatments. The AUC values ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$) for THC show an approximate 8 to 10-fold difference between the lowest and highest subject values while the difference for CBD was approximately 3.5 to 4-fold. Differences in C_{max} were 20 to 30 fold for THC and approximately 14-fold for CBD. Intra-subject differences in values for THC between treatments were smaller though differences in C_{max} of up to 5-fold and 3-fold in AUC ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$) were observed. Other than a single isolated significant difference in T_{max} there were no significant differences in pharmacokinetic parameters between the CBD:THC and High THC formulations. The bioavailability of THC appears to be greater than that of CBD.

Mean intoxication scores on both CBME treatments were very low

throughout the observation period. The majority of subjects scored zero for the majority of assessment points and there were few scores greater than three on the Box Scale 11 (BS-11). Recorded intoxication scores do not seem to show a direct relationship to plasma concentrations of THC and/or 11-hydroxy-THC either within or between subjects. The time of intoxication scores in individual subjects do not seem to relate consistently with the timing of increases in plasma concentrations or maximal concentrations of THC or 11-hydroxy-THC. Neither is there an apparent relationship between subjects reporting intoxication and those with the highest plasma levels of THC or 11-hydroxy-THC.

No subjects withdrew from the study as a result of adverse events and both active and the placebo test treatments were well tolerated. The treatment with the least number of treatment related adverse events was placebo. High THC and CBD:THC had a greater number of subjects who experienced intoxication type adverse events and application site type reactions. The most common overall adverse event experienced was throat irritation, followed by dizziness, somnolence, oral paraesthesia and then headache. All the events were mild and only two events needed any treatment. There were no clinically significant changes from baseline for haematology, biochemistry, vital signs or ECGs.

There was wide inter- and intra-subject variability in pharmacokinetic parameters with up to 10-fold differences in THC AUC between subjects and even greater differences in C_{max}. Results suggest that there are no overall statistically significant differences between the pharmacokinetic parameters of High THC and CBD:THC other than a delay in T_{max}. Considering the wide inter- and intra-subject variability in pharmacokinetic parameters including T_{max} this is unlikely to be clinically important in a medication that is self titrated by the patient.

KEYWORDS. Cannabinoids, cannabis, THC, cannabidiol, medical marijuana, pharmacokinetics, pharmacodynamics, multiple sclerosis, botanical extracts, alternative delivery systems, harm reduction

INTRODUCTION

Cannabis plants (*Cannabis sativa*) contain approximately 60 different cannabinoids (Association 1997) and in the UK, oral tinctures of cannabis were prescribed until cannabis was made a Schedule 1 con-

trolled substance in the Misuse of Drugs Act, 1971. The prevalence of recreational cannabis use increased markedly in the UK after 1960, reaching a peak in the late 1970s. This resulted in a large number of individuals with a range of intractable medical disorders being exposed to the drug, and many of these discovered that cannabis could apparently relieve symptoms not alleviated by standard treatments. This was strikingly the case with certain neurological disorders, particularly multiple sclerosis (MS). The black market cannabis available to those patients is thought to have contained approximately equal amounts of the cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Baker, Gough, and Taylor 1983). The importance of CBD lies not only in its own inherent therapeutic profile but also in its ability to modulate some of the undesirable effects of THC through both pharmacokinetic and pharmacodynamic mechanisms (McPartland and Russo 2001). MS patients claimed beneficial effects from cannabis in many core symptoms, including pain, urinary disturbance, tremor, spasm and spasticity (Association 1997). The MS Society estimated in 1998 that up to 4% (3,400) of UK MS sufferers used cannabis medicinally (Lords 1998).

Cannabinoid clinical research has often focussed on synthetic analogues of THC, the principal psychoactive cannabinoid, given orally. This has not taken the possible therapeutic contribution of the other cannabinoid and non-cannabinoid plant components into account, or the slow and unpredictable absorption of cannabinoids via the gastrointestinal tract (Agurell et al. 1986). Under these conditions it has been difficult to titrate cannabinoids accurately to a therapeutic effect. Research involving plant-derived material has often reported only the THC content (Maykut 1985) of the preparations, making valid comparisons between studies difficult. GW Pharma Ltd (GW) has developed cannabis based medicine extracts (CBMEs) derived from plant cultivars that produce high and reproducible yields of specified cannabinoids. CBMEs contain a defined amount of the specified cannabinoid(s), plus the minor cannabinoids and also terpenes and flavonoids. The specified cannabinoids constitute at least 90% of the total cannabinoid content of the extracts. The minor cannabinoids and other constituents add to the overall therapeutic profile of the CBMEs and may play a role in stabilising the extract (Whittle, Guy, and Robson 2001). Early clinical studies indicated that sublingual dosing with CBME was feasible, well tolerated and convenient for titration. The concept of self-titration was readily understood by patients and worked well in practice. Dosing patterns tended to resemble those seen in the patient controlled analgesia

technique used in post-operative pain control; with small doses administered as and when patients require them, up to a maximal rate and daily limit (Pharmaceuticals 2002). The Phase 2 experience has supported some of the wide-range of effects reported anecdotally for cannabis. It has also shown that for most patients the therapeutic benefits of CBMEs could be obtained at doses below those that cause marked intoxication (the 'high'). This is consistent with experience in patients receiving opioids for pain relief, where therapeutic use rarely leads to misuse (Porter and Jick 1980; Portenoy 1990). Onset of intoxication may be an indicator of over-titration. However the range of daily dose required is subject to a high inter-individual variability.

SATIVX (1:1 THC:CMD CBME) was administered as an oromucosal spray, and contains an equal proportion of THC and CBD, similar to the cannabinoid profile of the cannabis thought to be most commonly available on the European black market (Porter and Jick 1980; Portenoy 1990). The High-THC CBME was administered as an oromucosal spray, and contains over 90% of cannabinoids as THC. Placebo was administered as sublingual liquid spray and was used as a reference treatment to reduce bias.

GWPK0215 was a Phase I clinical study that primarily aimed to assess the PK profiles of each test treatment. It was also designed to assess safety and tolerability of the test treatments.

Primary objectives of this study were to assess the PK characteristics of CBME when administered sublingually in different ratios, to determine if the PK profiles of THC and its metabolite, 11-hydroxy-THC, are different when administered sublingually in different formulations, and to characterise the PK profile of CBD when administered with THC in equal amounts. Secondary objectives were to determine if there is a correlation between intoxication levels and plasma concentrations of THC and/or its metabolite 11-hydroxy-THC, and also to assess safety and tolerability of CBME when administered sublingually.

OVERALL STUDY DESIGN AND PLAN–DESCRIPTION

The study was a double-blind, three-period, three-way randomised crossover using single doses of 10 mg THC, 10 mg CBD + 10 mg THC and placebo. The test treatment was administered sublingually as a liquid spray according to the pre-determined randomisation scheme. The washout period between each dose was six days.

High THC CBME was formulated in 50% ethanol (Eth), 50% propylene glycol (PG) at a concentration of 25 mg THC per ml of Eth:PG with peppermint flavouring. It was delivered via pump action spray at 100 µl per actuation

SATIVEX (1:1 THC:CBD CBME) was formulated in 50% ethanol (Eth), 50% propylene glycol (PG) at a concentration of 25 mg CBD + 25 mg THC per ml of Eth:PG with peppermint flavouring. It was delivered via pump action spray at 100 µl per actuation. Placebo was formulated as Eth:PG in a 50:50 ratio with peppermint flavouring delivered via pump action spray at 100 µl per actuation.

Subjects were required to undergo a pre-study screen no more than 21 days prior to first dose administration to determine their eligibility to take part in the study. Only those subjects who were healthy and complied with all the study requirements were deemed eligible for participation.

These test treatments were chosen as they were the formulation and treatments that were used in the GW Pharmaceuticals clinical programme. The dose administered in this study (10 mg CBD and/or 10 mg THC) was chosen as this is a high single dose of the test treatment when used by patients in a self-titrated regime and is known to be well tolerated by normal healthy subjects.

A randomised cross-over design was chosen to enable both inter- and intra-subject comparisons of PK and pharmacodynamic data and to reduce period effect. The study was double-blind to ensure no bias could be introduced when assessing adverse events (AEs) and pharmacodynamic effects.

A six-day washout was chosen to ensure all cannabinoids were below the limit of quantification and eased the scheduling of the study in the clinical unit.

GW specified that only subjects with previous experience with the effects of cannabis be included in this trial to ensure that subjects recognised the adverse effects (in particular the 'recreational high') they may experience as a result of being dosed with the test treatments.

For inclusion in the study subjects were required to fulfil ALL of the following criteria:

i. Adult male aged between 18 and 50 years and BMI of between 19 and 30 kg/m^2.
ii. Had given written informed consent.
iii. Had experienced the effects of cannabis more than once.

Subjects were deemed not acceptable for participation in the study if any of the following criteria applied:

i. Had a presence of cardiovascular, haematological, hepatic, gastro-intestinal, renal, pulmonary, neurological or psychiatric disease.
ii. Had a history or presence of schizophrenic-type illness.
iii. Had a history or presence of drug or alcohol abuse in the past 12 months.
iv. Had been hospitalised in the three months prior to dosing.
v. Had lost or donated > 400 ml of blood in the three months prior to dosing.
vi. Had participated in a clinical trial in the three months prior to dosing.
vii. Had a history or presence of allergies to cannabis and/or its metabolites.
viii. Were taking or had taken a course of prescribed medication in the four weeks prior to dosing.
ix. Were taking or had taken over-the-counter medication, excluding paracetamol and/or vitamins but including mega dose vitamin therapy, within the week before administration of the first dose.
x. Had blood and/or urinalysis results at screening, which, in the opinion of the Principal Investigator were clinically significant.
xi. Had a resting blood pressure (BP) of > 150/90 mmHg or < 90/50 mmHg and a pulse of > 100 beats per minute (BPM) or < 40 BPM.
xii. Had an ECG which, in the opinion of the Principal Investigator was clinically significant.
xiii. Smoked ≥ 5 cigarettes or used the equivalent in tobacco per day.
xiv. Regularly consumed > 28 units of alcohol per week.

Subjects were required to agree to the following:

i. Using barrier methods of contraception during and for three months after completion of the study.
ii. Abstaining from consuming all foods and beverages containing caffeine and/or alcohol for 36 h before until the end of each confinement period.
iii. Abstaining from taking any medications (prescription and/or over-the-counter) and drugs, for the duration of the study.

iv. Not smoking or using tobacco products during each confinement period.
v. Not donating blood in the three months after completion of the study.
vi. Not participating in another clinical trial for 3 months after completion of this one.

The subjects were free to withdraw from the study without explanation at any time and without prejudice to future medical care. Subjects may have been withdrawn from the study at any time if it was considered to be in the best interest of the subject's safety.

A single dose of 10 mg THC, a single dose of 10 mg CBD + 10 mg THC and a single dose of placebo were administered sublingually to each of 24 subjects on three separate occasions in a randomised manner. Each single dose consisted of a series of four actuations of 100 µl volume each (2.5 mg CBD and/or 2.5 mg THC per actuation) and each actuation was administered five minutes apart. Each subject received all of the test treatments once. Each vial was identified with no less than study number, subject number, period number, batch number and expiry date.

Subjects were randomised to a dose sequence using a Williams Square Design provided by GW. All subjects were randomised to receive a single dose of each of the test treatments once in each of the three periods.

The dosing regime and doses chosen are well tolerated by both subjects and patients. The dose given has been previously used in other GW Phase I studies and has been shown to produce both quantifiable drug concentrations in plasma and pharmacodynamic effects.

The subjects were dosed in three groups of eight subjects (Group 1; Subjects 101-108, Group 2; Subjects 109-116 and Group 3; Subjects 117-124). The test treatments were administered in the morning of each dosing day according to the randomisation scheme. Subjects were dosed in the morning to allow blood samples to be taken and procedures to be carried out up to 24 h post-dose with minimal disruption to the subjects during the night. A minimum of six days washout between each dose was specified as previous data and drug of abuse screens have indicated that concentrations of each cannabinoid from a single dose of CBME are below the limit of quantification by this time.

The study was double-blind. Unblinding envelopes were retained at the study site and a duplicate set was retained at GW. All subjects completed the study without experiencing any serious adverse events (SAEs)

and unblinding was not required. Upon completion of the in-life phase of the study all unblinding envelopes were returned to GW intact.

Only one subject (Subject 101) took medication during the study.

Subjects were dosed by the Principal Investigator or suitably trained designee. Subjects were instructed to allow each spray of the study formulation to absorb under their tongue and not to swallow, if possible, until the drug had been absorbed. The actual time of administration of each actuation was recorded in the CRF (Case Report Form) and the dosing procedure was witnessed by a dose verifier. All subjects received all of the scheduled doses and there were no deviations from the dosing regimen.

Only those subjects who were healthy and complied with all the study requirements were deemed eligible for participation. The screening procedures comprised the following assessments/measurements: The subjects' date of birth, sex, race, height, weight, BMI, previous cannabis experience, tobacco and alcohol habits were recorded. Subjects were asked to provide details of any drugs, vitamins or medications they had taken in the four weeks prior to screening or were taking at the time of screening.

Details of their previous medical history were also recorded. Subjects underwent a physical examination to determine if there were any abnormalities in any body systems. BP (systolic/diastolic) and pulse were measured after the subject had been seated for no less than 2 minutes. Oral temperature was also measured. A 12-lead ECG (electrocardiogram) was taken for each subject. At least the following ECG parameters were recorded: HR (heart rate), PR, QT_c and QRS intervals. The ECGs were expertly read by Cardio Analytics for ventricular rate, PR interval, QRS duration and QT interval.

Subjects were required to provide a urine sample for routine urinalysis to include protein glucose, ketones, bilirubin, nitrites, blood, urobilinogen, haemoglobin (Hb), and Ph. Microscopy was required to be carried out on any abnormal samples. The samples provided were also screened for alcohol and drugs of abuse, including methadone, benzodiazepines, cocaine, amphetamines, THC, opiates and barbiturates

A blood sample was taken in an EDTA blood tube for full haematology analysis. A blood sample was taken in a gel blood tube for clinical chemistry analysis. The following clinical chemistry parameters were measured: sodium, potassium, urea, creatinine, total bilirubin, alkaline phosphatase, total protein, calcium, gamma glutamyl transferase (GGT), albumin, aspartate aminotransferase (AST), alanine aminotransferase

(ALT). A blood sample was taken in a gel blood tube to screen for the serological presence of past or present Hepatitis B and/or C.

Subjects were required to arrive at the clinic approximately 12 hours prior to dosing for each study period. Each subject's health status was updated and pre-dose procedures (health status update, BP and pulse, alcohol and drug of abuse screen, ECG, Box Scale-11 and blood sample for plasma concentration analysis) were carried out. Only subjects who complied with the requirements of the study were accepted for inclusion in the study.

Blood samples (5 ml) for pharmacokinetic analysis were collected into lithium heparin blood tubes via indwelling cannula or individual venipuncture. Samples were placed immediately into an ice bath until centrifuged (3000 RPM for 10 min at 4°C). The resultant plasma was decanted into two identical pre-labelled silanised amber glass plasma tubes and stored in a freezer at −20°C until shipped to the analytical laboratory.

Blood samples were collected pre-dose and at the following times post start of dosing: 15, 30 and 45 m and 1 h, 1 h 10 m, 1 h 20 m, 1 h 30 m, 1 h 40 m, 1 h 50 m, 2 h, 2 h 15 m, 2 h 30 m, 3, 6, 9, 12 and 24 h post first actuation in each period. Plasma concentrations of CBD, THC and 11-hydroxy-THC were measured in each plasma sample.

SAFETY ASSESSMENTS

Each subject was required to provide a urine sample for a urine drug screen at check in for each dosing period. The drug screen was required to be negative for all drugs pre-dose Period 1. For Periods 2 and 3, positive THC results may have occurred due to administration of test treatment in the previous period and therefore screening for THC was not carried out post Period 1. The urine sample was required to be negative for all other drugs for the subject to be eligible to continue.

The urine sample provided at check-in for each study period for the drug screen was also screened for alcohol. All subjects were required to have a negative alcohol screen to be considered eligible to continue in the study.

12-Lead ECGs were taken for each subject at the following times: pre-dose, 1, 2, 12 and 24 h post-dose. The QT_c intervals for all ECGs were read manually by Cardio Analytics, ITTC Building 2, Tamar Science Park, 1 Davy Road, Derriford, Plymouth, PL6 8BX. Subjects'

blood pressure and pulse were measured pre-dose and at 15, 30 and 45 min, 1, 1.5, 2, 3, 6, 9, 12 and 24 h post start of dosing.

Adverse Effects

Subject health was monitored continuously throughout the study for AEs and pharmacodynamic effects and subjects were encouraged to inform the clinical staff of any changes in their health as soon as possible. In addition, subjects' health was monitored by asking non-leading questions pre-dose and at the following times post-dose: 15, 30 and 45 min, 1, 1.5, 2, 2.5, 3, 6, 9, 12 and 24 h post-dose. Any concomitant medications taken during the study were recorded in the subjects CRF.

Box Scale-11 for Intoxication

Subjects were required to complete a Box Scale 11 (BS-11) to describe how intoxicated they were feeling at the following times: pre-dose, 15 m, 30 m, 45 m, 1 h, 1 h 30 m, 2 h, 3 h, 6 h, 9 h, 12 h and 24 h post start of dosing.

Palatability/Dose Questionnaire

As soon as possible after dosing, subjects were asked to complete a questionnaire about the palatability and sensation of the test treatment experienced during and immediately after dosing.

Food and Beverages

A standard low fat breakfast approximately 30 min before dosing for each subject. From 15 min prior to 15 min post-dosing, subjects were required to abstain from consuming food and beverages. Thereafter, decaffeinated beverages and snacks, e.g., digestive biscuits, were available *ad libitum* throughout each confinement period. Subjects were provided with standard meals at approximately 4 and 10 h post-dose (lunch and dinner, respectively) (Table 1).

Check-Out Procedures

After completion of the 24 h study procedures at the end of Periods 1 and 2 and if deemed by the Investigator to be well enough to leave, subjects were discharged from the clinical unit. Prior to discharge, any on-

TABLE 1. Menu

*Day 1**			*Day 2*
Breakfast	*Lunch*	*Dinner*	*Breakfast*
Orange juice Cereals toast with butter & preserves tea/coffee** orange/lemon	Jacket potato Cheese Coleslaw and Salad Yoghurt tea/coffee** orange/lemon	Chicken Quorn Fillet (v) Roast Potatoes peas and carrots gravy gravy (v) Peach melba ice cream sundae tea/coffee** orange/lemon	Orange juice Cereals toast with butter & preserves tea/coffee** orange/lemon

NB: At each admission (Day -1) subjects were permitted 2 digestive biscuits, decaffeinated tea/coffee and orange/lemon
*Digestive Biscuits and Drinks available throughout the day ** decaffeinated v = vegetarian

going AEs were updated and follow up arranged if required. Prior to Period 3 discharge, subjects were required to undergo a physical examination, blood samples were taken for haematology and clinical chemistry, urinalysis was carried out, a 12-lead ECG was taken and vital signs recorded as per screening. Ongoing AEs were updated and if required arrangements were made to follow up with the subjects after they left the clinical unit.

DATA QUALITY ASSURANCE

Study Monitoring

All details regarding the study were documented within individual CRFs provided by GW for each subject. All data recorded during the study were checked against source data and for compliance with Good Clinical Practice (GCP), internal Standard Operating Procedures (SOPs), working practices and protocol requirements. Monitoring of the study progress and conduct was ongoing throughout the study. Monitoring was conducted by the Clinical Department of GW and was conducted

according to GW SOPs. An initiation visit was carried out prior to the start of the study to train site clinical staff on CRF completion, dosing and AE procedures. Training was provided by GW throughout the study as required. Haematology and clinical chemistry analysis were carried out by Leicester General Hospital

Investigator Responsibilities

The Investigator was responsible for monitoring the study conduct to ensure that the rights of the subject were protected, the reported study data were accurate, complete and verifiable and that the conduct of the study was in compliance with ICH GCP. At the end of the study the Principal Investigator reviewed and signed each CRF declaring the data to be true and accurate. If corrections were made after review the Investigator acknowledged the changes by re-signing and dating the CRF.

Clinical Data Management

All study data were collected by GW, who were responsible for evaluation, collation and analysis. Data were subject to quality control procedures. All data were double entered into a Microsoft® Excel 2000 spreadsheet with 10% quality control checks according to GW SOPs. Clinical Quality Audits were carried out by the GW Quality Assurance Department, two Quality Assurance evaluation were carried out and the Pharmacovigilance function was the subject of an internal process audit.

Pharmacokinetic Analysis

All subjects who were dosed and had no more than two missed blood samples were deemed evaluable for, and were included in, PK analyses. All analyses and summary statistics were carried out and derived using SAS v8. All p-values quoted are two-sided. Summary statistics were calculated for each mean PK parameter and treatment (arithmetic mean, N, SD, CV%, minimum, maximum for all parameters and additionally the geometric mean for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}). AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were natural log transformed prior to analysis, T_{max} and $t_{1/2}$ were analysed untransformed. For the analytes THC and 11-hydroxy-THC, each parameter was analysed using analysis of variance (ANOVA) with subject and treatment as factors (for High THC and CBD:THC). Least square means are presented for each test treatment. Point estimates of the differences between least square means are presented with

the corresponding 95% confidence intervals. For log transformed variables, the contrasts were also back transformed to provide ratios and corresponding 95% confidence intervals. For the analyte CBD which was measurable for only the CBD:THC test treatment, the data are presented descriptively only. K_{el} is presented descriptively only.

Pharmacodynamic Analysis

All subjects who completed at least one study period were evaluable for pharmacodynamic analysis. Intoxication, measured by Box Scale-11, was summarised by treatment group. Means and standard deviations were also calculated.

SAFETY ANALYSIS

Adverse Events

AEs were coded by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. These are summarised by test treatment for treatment emergent all causality and treatment emergent treatment related AEs showing the number of subjects with at least one AE and the number of subjects with at least one AE by preferred term within system organ class.

Clinical Laboratory Tests

Laboratory data collected pre- and post-study are summarised descriptively at each of the two time-points and also as the change post-study compared to pre-study.

Concomitant Medications

Subject 101 took concomitant medications between Periods 2 and 3.

Blood Pressure, Pulse and Oral Temperature

Vital signs (pulse, systolic BP, diastolic BP and oral temperature) were monitored. BP and pulse are presented descriptively at each time point up to 12 h post-dose for each test treatment.

12-Lead ECG

ECG parameters (HR, PR interval, QT interval, QT_c and QRS width) were monitored descriptively (N, mean, SD, median, minimum, maximum) pre-study and at each time point up to 12 h post-dose for each test treatment. In addition, QT_c values were classified as either normal, borderline or prolonged. For QT_c, absolute values and changes from pre-dose were categorised as borderline, normal, prolonged according to Committee for Proprietary Medicinal Products (CPMP) guidelines.

Palatability Questionnaire

Each question of the palatability questionnaire was been presented descriptively using frequency tables for each test treatment.

Determination of Sample Size

No formal sample size calculation was carried out for this study. The number of subjects is considered to be sufficient to provide information on the pharmacokinetics of the two formulations.

Changes in the Conduct of the Study or Planned Analyses

A Statistical Analysis Plan (SAP) was not produced prior to statistical analysis as detailed in the protocol and the statistical analyses were carried out as indicated in the protocol with the exception of the following:

1. The mean profile with time curve for vital signs for each treatment is not presented.
2. The data was not summarised using the AUEC for blood pressure and pulse rate calculate using the trapezoidal rule.
3. The AUEC was not analysed using the analysis of variance with factors for subject, period and treatment

STUDY SUBJECTS

Disposition of Subjects

Twenty-four healthy male subjects were required to complete the study in its entirety. Twenty-four subjects were randomised and all of

those subjects completed the study. No subjects withdrew from the study and no replacements were required.

Protocol Deviations

Three significant deviations occurred during the study as follows.

1. Post-study oral temperature was not recorded in accordance with ICH GCP, therefore the reliability of the data was not known and was not reported. All subjects were assessed by a physician prior to discharge and all were deemed to be well.
2. On May 18, 2002 (Group 2, Period 2) some blood samples for plasma concentration analysis were taken in sodium heparin blood tubes in error. The analytical laboratory carried out validation testing for use of the sodium heparin tubes and confirmed that changing the blood collection tubes from lithium heparin to sodium heparin did not alter the extraction efficiency or change in analytical methodology required.
3. Subject 101 took two single oral doses (400 mg each) of ibuprofen tablets on two consecutive days (May 18 and 19, 2002) for coryza. This was during the restriction period between Periods 2 and 3. Investigator's judgement was made and the subject was deemed eligible to continue in the study.

These protocol deviations were not considered to affect the integrity of the study.

Plasma Concentration, Pharmacokinetic, and Pharmacodynamic Evaluation

All twenty-four subjects (101 to 124) who were randomised completed the study. Subjects were considered evaluable if no more than one blood sample per period was missed. No blood samples were missed therefore all subjects were included in the data analysis.

All subjects included in the study complied with all demographic and baseline requirements. Each test treatment was administered by suitably trained study site clinical staff. No deviations to the dosing regimen were noted for any subject throughout the study.

INDIVIDUAL PLASMA CONCENTRATION DATA, PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

Analysis of Plasma Concentration Results

Plasma samples were analysed for CBD, THC and 11-hydroxy-THC according to the analytical protocol (Figure 1). Plasma concentration results are shown in tabular form (Table 2) and concentration-time graphs produced from these data (Figures 2-6).

The Lower Limit of Quantification (LLOQ) for this study was 0.1 ng/ml. The actual values measured were used when creating graphs.

Mean plasma concentrations of the relevant cannabinoids for the formulations are summarised in Table 2.

Mean plasma concentrations show that following administration of both High THC and CBD:THC formulations (Figure 2, Figure 3), THC was detectable in plasma in measurable concentrations 30-45 min after dosing, although subjects showed quite wide variability with both formulations (15-70 min). At all time points up to 180 min after dosing, mean concentrations of THC were greater following the High THC formulation (Figure 2) than CBD:THC (Figure 3). Mean 11-hydroxy-THC plasma levels (Figure 4, Figure 5) seemed generally to reflect levels of THC and were similarly greater following High THC (Figure 4) at most time points up to 180 min.

Mean plasma levels of CBD were above the level of detection about 45 min after dosing and were approximately 30-50% lower than the cor-

FIGURE 1

The following PK parameters were calculated for CBD, THC and 11-hydroxy-THC:

T_{max}	Time to the maximum measured plasma concentration.
C_{max}	Maximum measured plasma concentration over the time span specified.
$t_{1/2}$	Putative effective elimination half life (the initial descending portion of each plasma concentration-time graph).
$AUC_{0\text{-}t}$	The area under the plasma concentration versus time curve, from time zero to 't' (where t = the final time of positive detection, $t \leq 24$ h) as calculated by the linear trapezoidal method.
$AUC_{0\text{-}\infty}$	The area under the plasma concentration versus time curve from zero to t calculated as $AUC_{0\text{-}t}$ plus the extrapolated amount from time t to infinity.
K_{el}	Elimination rate.

TABLE 2. Mean Plasma Concentration Data

Time (min)	*Analyte*				
	CBD	*THC*		*11-Hydroxy-THC*	
	Test Treatment				
	CBD:THC	*High THC*	*CBD:THC*	*High THC*	*CBD:THC*
0	0.00	0.01	0.00	0.00	0.00
15	0.00	0.02	0.01	0.01	0.00
30	0.05	0.13	0.06	0.22	0.10
45	0.21	0.47	0.30	0.81	0.53
60	0.38	0.77	0.61	1.19	1.01
70	0.39	1.11	0.61	1.34	1.06
80	0.52	1.26	0.75	1.57	1.23
90	0.62	1.65	0.89	1.86	1.44
100	0.84	2.15	1.21	2.33	1.59
110	1.21	2.60	1.78	2.53	1.73
120	1.15	2.82	1.69	2.65	1.90
135	1.27	2.87	1.80	2.45	2.14
150	1.37	2.93	1.93	2.77	2.52
180	2.04	4.02	2.72	3.51	2.93
360	1.34	1.17	1.82	1.74	2.38
540	0.49	0.32	0.51	0.67	1.02
720	0.24	0.19	0.21	0.44	0.58
1440	0.00	0.03	0.01	0.16	0.16

responding levels of THC (Figure 6). Again there was quite wide variability between subjects with the time of first measurable concentration ranging from 30 to 135 min.

Following administration of High THC CBME, no subject had measurable concentrations of CBD at any time point. Following placebo, a single blood sample (60 min) from Subject 115 recorded levels of THC, CBD and 11-hydroxy-THC. Also, on the placebo dosing day, Subject 121 had measurable concentrations of THC pre-dose and at all time points post-dose. 11-Hydroxy-THC was also detected pre-dose and all time point up to 3 h post-dose. Subject 115 also had one value for THC (0.19 ng/ml at 60 min) and 11-hydroxy-THC (0.23 ng/ml at 60 min) fol-

FIGURE 2. GWPK0215 Mean Plasma THC Concentrations Following Administration of High THC

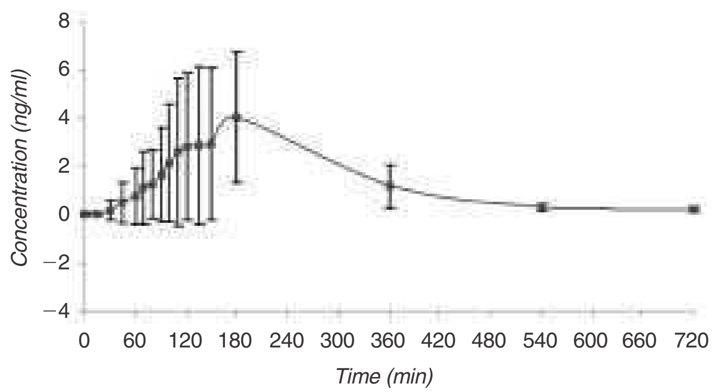
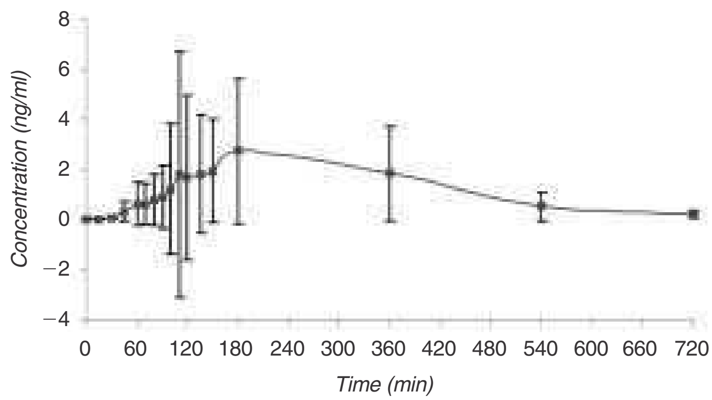


FIGURE 3. GWPK0215 Mean Plasma THC Concentrations Following Administration of CBD:THC



lowing administration of the placebo treatment which was above the LLOQ. The placebo treatment for subjects 115 and 121 was Period 3 and therefore followed previous High THC and CBD:THC dosing.

Analysis of Pharmacokinetic Parameters

PK parameters were calculated using WinNonlin® Professional 3.1. The model used was a non-compartmental, linear trapezoidal analysis.

FIGURE 4. GWPK0215 Mean Plasma 11-Hydroxy-THC Concentrations Following Administration of High THC

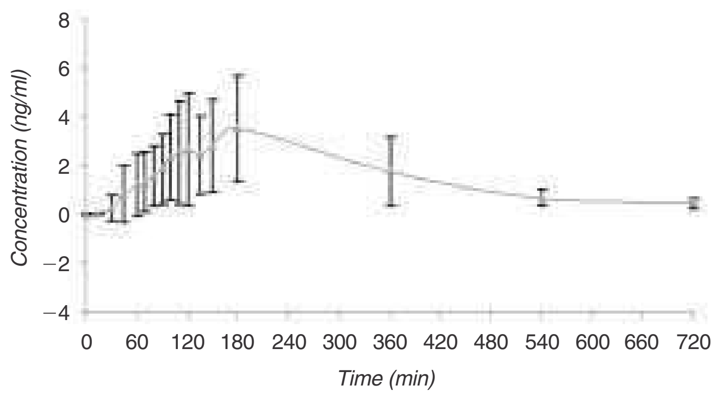
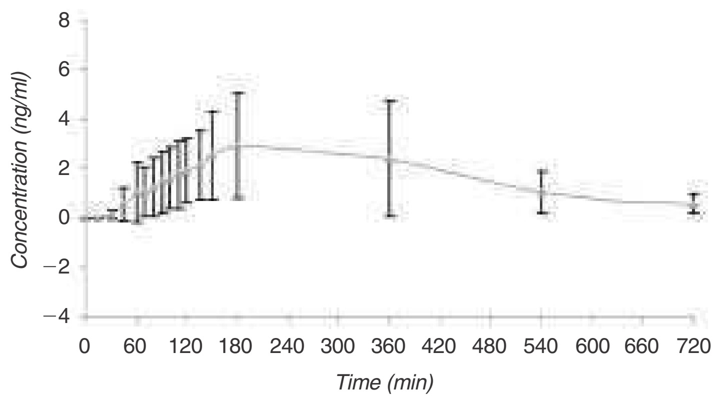


FIGURE 5. GWPK0215 Mean Plasma 11-Hydroxy-THC Concentrations Following Administration of CBD:THC



Values below the LLOQ are not considered reliable and therefore were not used when calculating PK parameters. Mean values are presented in Table 3.

Following dosing with the CBD:THC test treatment the mean C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of CBD were lower than the corresponding mean results for THC though T_{max} was similar. The $t_{1/2}$ of CBD (108.72 min) was longer than the $t_{1/2}$ of THC (84.23 min).

The PK values for each individual showed considerable inter- and

FIGURE 6. GWPK0215 Mean Plasma CBD Concentrations Following Administration of CBD:THC

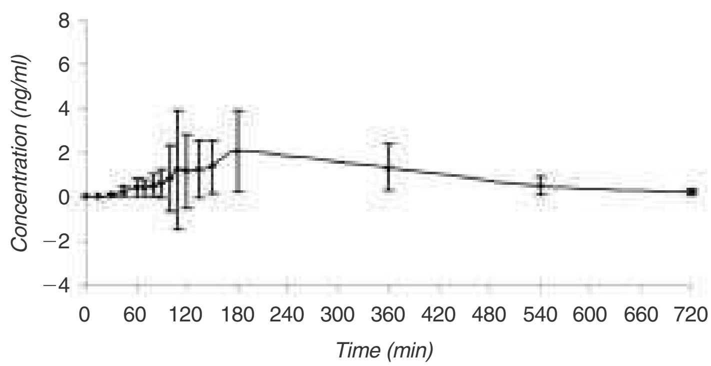


TABLE 3. Mean Pharmacokinetic Parameters

Treatment	T_{max} (min)	C_{max} (ng/ml)	$t_{1/2}$ (min)	$AUC_{0\text{-}t}$ (min*ng/ml)	$AUC_{0\text{-}\infty}$ (min*ng/ml)
	Mean Pharmacokinetic Parameters for CBD				
CBD:THC	253	3.33	108.72	680.61	718.46
	Mean Pharmacokinetic Parameters for THC				
High THC	188	5.66	73.09	987.47	1005.90
CBD:THC	263	4.90	84.23	894.80	918.81
	Mean Pharmacokinetic Parameters for 11-Hydroxy-THC				
High THC	179	4.81	109.38	1300.47	1334.41
CBD:THC	230	4.49	130.11	1423.20	1463.67

Mean C_{max}, $t_{1/2}$, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of both THC and 11-hydroxy-THC were not statistically significantly different following the High THC and CBD:THC formulations. T_{max} of both THC and 11-hydroxy-THC was later following the CBD:THC than High THC formulation though only the difference in THC T_{max} reached statistical significance ($p = 0.014$).

intra-subject variation in all parameters. The variability appeared to be greater for THC than for CBD. The AUC values ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$) for THC show an approximate 8 to 10-fold difference between the lowest and highest subject values while the difference for CBD was approximately 3.5 to four-fold. Differences in C_{max} were 20 to 30-fold for THC and approximately 14-fold for CBD. Intra-subject differences in individual values for THC between treatments were smaller though differ-

ences in C_{max} of up to 5-fold and 3-fold in AUC ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$) were observed.

Analysis of Intoxication Results

For each test treatment period, intoxication was measured using BS-11 with a score of zero indicating no intoxication and a score of 10 indicating maximum intoxication. Mean intoxication results are presented in Table 4.

On the placebo day Subject 114 scored pre-dose intoxication at a level of 5 and from 45-90 min scored a level of 6 then 5 for the remainder of the 24 h period. Two other subjects (108 and 124) scored an increased level intoxication of 1 at some time points (45-60 min and 15-60 min, respectively). Mean levels of intoxication remained low for both active test treatments throughout each 24 h post-dose period.

Following administration of High THC CBME, individual intoxication scores were below five. Seven subjects scored no intoxication at all assessment points (no score > zero). Seven subjects had at least one

TABLE 4. Mean Intoxication Following Administration of Each Test Treatment

Time (min)	*Mean Intoxication*		
	Placebo	*High THC*	*CBD:THC*
0	0.2	0.0	0.0
15	0.3	0.3	0.2
30	0.3	0.4	0.2
45	0.3	0.5	0.3
60	0.3	0.5	0.5
90	0.3	0.5	0.6
120	0.2	0.6	0.8
180	0.2	0.9	0.8
360	0.2	0.7	1.2
540	0.2	0.2	0.4
720	0.2	0.0	0.1
1440	0.2	0.0	0.0

Mean levels of intoxication remained below 1 throughout the 24h period following placebo dosing. Mean intoxication scores on both test treatments were very low throughout the observation period with increased levels (mean score of 1) only between 60 and 360 minutes after dosing.

score of three or greater though in four subjects this was at a single assessment point. One subject (Subject 115) recorded a score of three or greater at two consecutive time points, Subject 101 recorded scores of three between 45 and 180 min post-dose and Subject 121 recorded scores of three or greater between 30 and 180 min post-dose. The highest individual intoxication score was five (Subject 121 at 45 and 60 minutes post-dose).

Following administration of CBD:THC, nine subjects scored no intoxication at all assessment points. Ten subjects had at least one score of three or greater though in five this was at a single assessment point. Five subjects (subjects 101, 111, 112, 113 and 116) recorded a score of three or greater at two consecutive time points. The highest individual intoxication score was 10 (Subject 112 at a single time point post-dose).

Recorded intoxication scores do not seem to show a direct relationship to plasma concentrations of THC and/or 11-hydroxy-THC either within or between subjects. The times of intoxication scores in individual subjects do not seem to relate consistently with the timing of increases in plasma concentrations or maximal concentrations of THC or 11-hydroxy-THC. Neither is there an apparent relationship between subjects reporting intoxication and those with the highest plasma levels of THC or 11-hydroxy-THC. The maximum intoxication score of 10 reported by Subject 112 occurred 360 minutes post-administration of CBD:THC. This maximal intoxication score was not associated with any report of AEs typical of intoxication (e.g., somnolence, dizziness). Vital signs at this time were only a little changed from pre-dose–pulse 68 (−4), systolic BP 106 (−16) diastolic BP 63 (−4) and do not suggest significant cannabinoid effects. However, the score of 10 coincided with a substantial increase in plasma levels of both THC (3.56 ng/ml) and 11-hydroxy-THC (3.96 ng/ml) compared with both the previous (0.21 and 0.48 ng/ml, respectively) and subsequent measurements (0.77 and 1.88 ng/ml, respectively) at which much lower intoxication scores were reported (0 and 3, respectively). On the day that the High THC was administered the highest intoxication score recorded by this subject was three at 6 h post-dose even though during this dosing period higher plasma levels of THC (2.45 ng/ml) were recorded compared with the CBD:THC test treatment. Plasma levels of 11-hydroxy-THC were a little lower on this occasion.

Analysis of Safety Parameters

For each of the BP and pulse parameters descriptive statistics (n, mean, SD, median, minimum and maximum) were presented at each

time point by test treatment. In addition, the calculations were performed for the absolute change from pre-dose. Mean values and mean changes from baseline were similar across all treatments.

Descriptive statistics (n, mean, SD, median, minimum and maximum) were recorded for the ECG parameters (heart rate, PR interval, QT interval and QRS width) pre-dose and at each time point by test treatment. ECG intervals were expertly read by Cardio Analytics for each of the parameters above. There were no notable changes in the ECG parameters.

Eight subjects (33%) rated the placebo test treatment as very unpleasant or unpleasant compared with 18 subjects (75%) for both the THC and CBD:THC treatments.

One subject (4%) thought the placebo treatment had an unpleasant smell compared with four (17%) subjects who thought the High THC treatment smelt unpleasant. Four (17%) subjects thought the CBD:THC smelt unpleasant and two (8%) very unpleasant. Eleven subjects (46%) for each treatment reported that they were unaware of the smell.

All three test treatments resulted in increased saliva produced with 13 subjects (54%) reporting more saliva following administration of placebo, 16 subjects (66%) with High THC and 17 subjects (71%) with CBD:THC.

The majority of subjects reported that they thought all or most of the test treatments were absorbed in the mouth. Only six subjects (25%) after placebo and High THC thought that some was swallowed and four subjects (17%) after CBD:THC reported some was swallowed.

Most subjects reported no other effects or sensations following administration of each test treatment. Four subjects (17%) reported other effects following administration of placebo, nine subjects (38%) following administration of High THC and 10 subjects (42%) following administration of CBD:THC.

The study was carried out in healthy subjects, none of whom were not taking a regular course of any other medication.

Plasma Concentration Conclusions

Mean plasma concentrations show that following administration of both High THC and CBD:THC formulations, CBD and/or THC were detectable in plasma in measurable concentrations 30-45 min after dosing, although individual subjects showed quite wide variability, 15 to 135 min, to appearance of measurable concentrations. At all time points up to 180 min after dosing mean concentrations of THC were greater

following the High THC formulation than CBD:THC. Concentrations of THC were also greater than corresponding concentrations of CBD following the CBD:THC treatment.

There was considerable individual variability in peak plasma concentrations (C_{max}) of both CBMEs. THC C_{max} ranged from 0.69 ng/ml to 14.2 ng/ml and from 0.75 ng/ml to 24.63 ng/ml for the High THC and CBD:THC formulations, respectively. CBD C_{max} following the CBD:THC formulation ranged from 0.96 ng/ml to13.64 ng/ml.

Following administration of High THC CBME, no subject had measurable concentrations of CBD at any time point. Following placebo, a single blood sample (60 min) from Subject 115 had recorded measurable levels of THC, CBD and 11-hydroxy-THC. This sample was re-analysed by the analytical laboratory, however the result may be due to an analytical anomaly. Also on the placebo dosing day Subject 121 had measurable concentrations of THC pre-dose and at all time points post-dose and 11-hydroxy-THC was also measured pre-dose and all time point up to 3 hours post-dose. The placebo treatment in this subject was Period 3 and therefore followed previous High THC and CBD:THC dosing. As there was no carryover from Period 1 to Period 2 in this subject it is unclear whether the THC detected on the placebo day is due to carryover from the previous treatment or a protocol violation in respect of abstention from cannabis.

Pharmacokinetic Conclusions

There were no statistically significant differences in mean C_{max}, $t_{1/2}$, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of both THC and 11-hydroxy-THC between the High THC and CBD:THC formulations. THC T_{max} was statistically significantly later following CBD:THC than High THC ($p = 0.014$) and this was the only statistically significant difference in PK parameters between the treatments. Following the CBD:THC formulation the C_{max} and AUC of CBD were lower than the corresponding results for THC and the $t_{1/2}$ of CBD (108.72 min) was longer than the $t_{1/2}$ of THC (84.23 min). The PK values for each individual show considerable inter- and intra-subject variation in all parameters. The variability appears to be greater for THC than for CBD. The AUC values ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$) for THC show an approximate 8 to 10-fold difference between the lowest and highest subject values while the difference for CBD was approximately 3.5 to 4-fold. Differences in C_{max} were 20 to 30 fold for THC and approximately 14-fold for CBD. Intra-subject differences in values

for THC between treatments were smaller though differences in C_{max} of up to 5-fold and 3-fold in AUC (AUC_{0-t} and $AUC_{0-\infty}$) were observed.

Other than a single isolated significant difference in T_{max} there were no significant differences in PK parameters between the CBD:THC and High THC formulations. It is unclear whether this significant difference reflects a true or spurious difference in the rates of absorption from the formulations, however, the difference is small and unlikely to be of clinical significance considering the high level of inter- and intra-subject variability in PK. The bioavailability of THC appears to be greater than that of CBD.

Intoxication Conclusions

Mean intoxication scores on both CBME treatments were very low throughout the observation period. The majority of subjects scored zero for the majority of assessment points and there were few scores greater than three on the 11 box scale. One subject recorded a maximal score of 10 at a single (6 h) assessment point following CBD:THC. No AEs were reported and vital signs showed only a slight change from pre-dose at this time, therefore it is uncertain that this reflects an accurate assessment. Recorded intoxication scores do not seem to show a direct relationship to plasma concentrations of THC and/or 11-hydroxy-THC either within or between subjects. The time of intoxication scores in individual subjects do not seem to relate consistently with the timing of increases in plasma concentrations or maximal concentrations of THC or 11-hydroxy-THC. Neither is there an apparent relationship between subjects reporting intoxication and those with the highest plasma levels of THC or 11-hydroxy-THC.

Palatability Conclusions

Both active test treatments, but not placebo, were considered by the majority of the subjects to have an unpleasant or very unpleasant taste. Therefore it can be concluded that the THC and/or CBD, and not the excipients, result in an increased incidence of unpleasant taste. The majority of subjects reported that they were not aware of a smell from the test treatment or that they thought it smelt neither pleasant or unpleasant. Therefore it can be concluded that for the majority of subjects THC and/or CBD in the test treatments used in this study do not have an unpleasant smell. All three test treatments were reported to have increased sa-

liva with a marginally higher incidence from the CBME containing treatments. Most subjects perceived that all or most of the test treatments were absorbed in the mouth.

Other Effects or Sensations

The incidence of other effects or sensations following administration of each test treatment was greater for the CBME treatments than for placebo though the majority of subjects on all treatments reported no such effects.

ADVERSE EVENTS (AES)

Brief Summary of Adverse Events

During the study 87 AEs were recorded in 20 subjects (Table 5) , and of these, 78 were considered to be related to the test treatment (Table 6). Following the administration of placebo, 5 subjects experienced treatment emergent treatment related AEs (Table 6). Following administration of the THC test treatment 16 subjects (66%) experienced treatment emergent treatment related AEs and 18 subjects (75%) experienced treatment emergent treatment related AEs following administration of CBD:THC (Table 6). All the AEs experienced were classified as mild and only one event (Subject 101, coryza) required treatment with medication. None of the subjects withdrew due to AEs. One AE in Subject 107 (left shoulder muscular strain) was lost to follow up.

The most common treatment emergent treatment related AE experienced was throat irritation (six subjects following administration of High THC and eight subjects following administration of CBD:THC), which was not experienced in the subjects during placebo treatment. Dizziness was the second most commonly experienced treatment emergent treatment related AE following the administration of High THC (six subjects). This was followed by somnolence, oral paraesthesia and headache.

Analysis of Adverse Events

Table 7 summarises the number of subjects who reported treatment emergent treatment related AEs by System Organ Class (SOC). There

TABLE 5. Summary of Adverse Events–Treatment Emergent All Causality

Event	*Placebo*	*High THC*	*CBD:THC*
No. of subjects with ≥ 1 event	6 (25.0%)	16 (66.7%)	18 (75.0%)
Eye disorders	0	1	0
Vision blurred		1	
Gastrointestinal disorders	1	9	14
Diarrhoea NOS			1
Glossitis	1		1
Nausea		2	2
Oral discomfort		1	1
Oral pain		1	1
Throat irritation		6	8
Tongue oedema			1
Vomiting NOS			1
General disorders and administration site conditions	2	2	1
Feeling of relaxation	2	1	
Lethargy	2	1	1
Injury, poisoning and procedural complications	1	1	2
Drug toxicity NOS		1	2
Splinter	1		
Musculoskeletal and connective tissue disorders	0	1	2
Muscle strain			1
Muscle twitching			1
Rib fracture		1	
Nervous system disorders	4	11	10
Burning sensation NOS		1	1
Dizziness	1	6	2
Dysgeusia			2
Headache NOS	2		3
Paraesthesia		1	
Paraesthesia oral NOS	1	2	3
Somnolence		4	3
Vasovagal attack (LLT Syncope vasovagal)		1	
Respiratory, thoracic and mediastinal disorders	0	3	2
Cough		1	
Rhinitis NOS		2	2
Skin and subcutaneous tissue disorders	1	0	0
Localised skin reaction	1		
Vascular disorders	0	1	0
Hot flushes NOS		1	

TABLE 6. Summary of Adverse Events–Treatment Emergent Treatment Related

Event	*Placebo*	*High THC*	*CBD:THC*
No. of subjects with ≥ 1 event	5 (20.8%)	16 (66.7%)	18 (75.0%)
Eye disorders	0	1	0
Vision blurred		1	
Gastrointestinal disorders	1	9	14
Diarrhoea NOS			1
Glossitis	1		1
Nausea		2	2
Oral discomfort		1	1
Oral pain		1	1
Throat irritation		6	8
Tongue oedema			1
Vomiting NOS			1
General disorders and administration site conditions	2	2	1
Feeling of relaxation	2	1	
Lethargy	2	1	1
Injury, poisoning and procedural complications	0	1	2
Drug toxicity NOS		1	2
Musculoskeletal and connective tissue disorders	0	0	1
Muscle twitching			1
Nervous system disorders	4	10	10
Burning sensation NOS		1	1
Dizziness	1	6	2
Dysgeusia			2
Headache NOS	2		3
Paraesthesia		1	
Paraesthesia oral NOS	1	2	3
Somnolence		3	3
Vasovagal attack (LLT syncope vasovagal)		1	
Respiratory, thoracic and mediastinal disorders	0	1	1
Cough		1	
Rhinitis NOS			1
Vascular disorders	0	1	0
Hot flushes NOS		1	

Note: treatment related = definitely, probably, possibly related

TABLE 7. Summary of Number of Subjects Who Experienced at Least One AE per SOC–Treatment Emergent Treatment Related

Event	*Placebo (n = 24)*	*High THC (n = 24)*	*CBD:THC (n = 24)*
No. of subjects with ≥ 1 event	5 (20.8%)	16 (66.7%)	18 (75.0%)
Eye disorders	0	1	0
Gastrointestinal disorders	1	9	14
General disorders and administration site conditions	2	2	1
Injury, poisoning and procedural complications	0	1	2
Musculoskeletal and connective tissue disorders	0	0	1
Nervous system disorders	4	10	10
Respiratory, thoracic and mediastinal disorders	0	1	1
Vascular disorders	0	1	0

were no deaths or serious AEs during the study, and no withdrawals attributed to AEs.

Clinical Laboratory Evaluation

All out of range values noted were considered by the Principal Investigator to be "not clinically significant." There were no clinically significant laboratory findings during the study. Several pre- and post-study results were out of the normal range but were not considered clinically significant. There were no statistically significant changes from pre- to post-study in any of the laboratory parameters. There were no notable changes, patterns or trends within the values from pre- and post-study in individual subjects.

Vital Signs, Physical Findings and Other Observations Related to Safety

There were no notable changes in diastolic BP during the study. There was a small transient increase in the mean pulse rate after 15 min during the High THC and CBD:THC periods. After three hours the mean systolic BP decreased by 10.3 mmHg during the High THC period, by 4.4 mmHg in the CBD:THC period, and 5.1 mmHg during the

placebo period. After 12 hours the mean pulse, systolic and diastolic BP values were close to the pre-dose values for all treatments.

No clinically significant changes in physical examination findings were noted from pre- to post-study. Only one change was noted in one subject, which began pre-dose and was not considered to be related to the test treatment. Each subject was asked about their previous medical history at screening. No events were considered to significant in relation to this study. There was no notable trend or pattern in the HR (BPM), PR Interval (msecs), QT_c (msecs), QRS width (msecs) in comparison to placebo. Two subjects had a borderline QT_c after dosing compared to pre-dose values. Subject 115 (CBD:THC period) had an increased QT_c of 41 msec (borderline) after 2 hours, this returned to normal after 12 h. Subject 119 (placebo period) had an increased QT_c of 35 msec (borderline) after 1 h and 33 msec after 12 h. In the opinion of the Investigator both borderline QT_c increases from pre-dose were considered not clinically significant. The ECGs taken during the study were read manually.

Safety Conclusions

The results of this study show that all three test treatments were well tolerated. CBD:THC had the most AEs followed by the THC group and then the placebo group. High THC and CBD:THC had a greater number of subjects who experienced intoxication type AEs and application site type reactions than placebo. The most common overall AE experienced was throat irritation, followed by dizziness, somnolence, oral paraesthesia and then headache. All the events were mild, one required treatment and one event was lost to follow-up.

DISCUSSION AND OVERALL CONCLUSIONS

All three test treatments administered in the study were well tolerated by all subjects. There were no AEs which resulted in any subject withdrawals from the study. Intoxication scores in the study were similarly low for both active treatments and did not appear to be directly related to plasma concentrations of THC and/or 11-hydroxy-THC and intoxication. There were no statistically significant differences in mean C_{max}, $t_{1/2}$, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of both THC and 11-hydroxy-THC between the High THC and CBD:THC formulations. THC T_{max} was statistically significantly later (262.7 mins compared with 187.7 mins) following

CBD:THC than High THC (p = 0.014) and this was the only statistically significant difference in PK parameters between the treatments. It is possible that the presence of CBD in the CBD:THC formulation delays the absorption of THC.

There was wide inter- and intra-subject variability in PK parameters with up to 10-fold differences in THC AUC between subjects and even greater differences in C_{max}. Results suggest that there are no overall statistically significant differences between the PK parameters of High THC and CBD:THC other than a delay in T_{max}. Considering the wide inter- and intra-subject variability in PK parameters, including T_{max}, this is unlikely to be clinically important in a medication that is self-titrated by the patient.

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Cannabis and Cannabis Based Medicine Extracts: Additional Results

Ethan Russo

SUMMARY. This study reviews results in recent human clinical trials with cannabis based medicine extract (CBME), THC or cannabis.

In a study performed at Queen's Square, London, both High THC and THC:CBD fixed ratio sublingual CBME demonstrated significant benefits on mean maximum cystometric capacity, mean daytime frequency of urination, frequency of nocturia, and mean daily episodes of incontinence in 11 multiple sclerosis patients with intractable lower urinary tract symptoms.

A Phase II clinical study in Oxford, England with 24 MS and intractable pain patients was performed as a consecutive series of double-blind, randomized, placebo-controlled single patient cross-over trials with sublingual CBME. Pain scores on visual analogue scales were significantly improved over placebo with both High THC and High CBD CBME. Subjectively, spasm was significantly improved with High THC and THC:CBD fixed ratio extracts. Spasticity was also subjectively improved with the High THC CBME. All three extracts significantly improved objective measures of spasticity, while the High THC and

Ethan Russo, MD, is a Clinical Child and Adult Neurologist, Clinical Assistant Professor of Medicine, University of Washington, and Adjunct Associate Professor of Pharmacy, University of Montana, 2235 Wylie Avenue, Missoula, MT 59802 USA (E-mail: erusso@montanadsl.net).

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THC:CBD fixed ratio CBME significantly improved objective measures of spasm.

In 34 intractable pain patients in Great Yarmouth, England, seven experienced substantial improvement over best available conventional treatment with CBME, 13 moderate, and eight some benefit. Many extended the range of their activities of daily living with acceptable levels of adverse effects.

Preliminary results of four Phase III clinical trials of CBME by GW Pharmaceuticals have revealed highly significant benefits in neuropathic pain in MS, pain and sleep disturbance in MS and other neurological diseases, multiple symptoms in MS, and neuropathic pain in brachial plexus injury, respectively. Most patients attained good symptomatic control with minimal side effects.

In Germany, a recent Phase II clinical trial has demonstrated significant benefit of oral THC in treatment of the tics of Tourette syndrome.

KEYWORDS. Medical marijuana, cannabis, alternative delivery systems, THC, cannabidiol, CBD, multiple sclerosis, chronic pain, Tourette syndrome, brachial plexus injury, pharmacotherapy

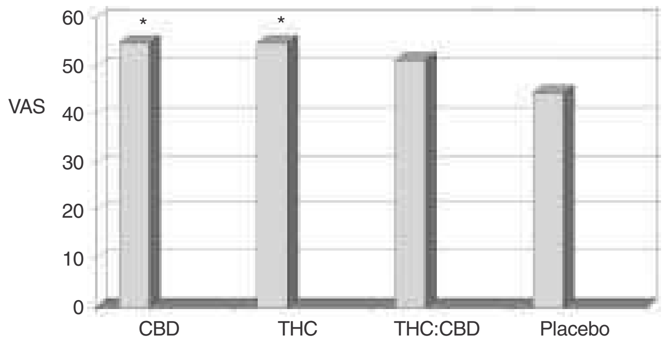
In 2001, interim results of a study of cannabis based medicine extracts (CBMEs) in bladder dysfunction were presented at the meeting of the International Association for Cannabis as Medicine (IACM) (Brady et al. 2001). A high-THC CBME and 1:1 THC:CBD CBME were compared to placebo in 17 multiple sclerosis patients with refractory lower urinary tract symptoms (LUTS). Eleven patients had evaluable data. Doses of up to 10 mg THC or 10 mg of THC and 10 mg of CBD were utilized. Mean maximum cystometric capacity (MCC) increased from 287 ml at baseline to 344 ml after eight weeks of CBME treatment (with 24 h of no drug). After 16 weeks, the bladder capacity measured 425 ml at maximum THC:CBD dosage. Mean daytime frequency or urination went from 9.3 to 7.5 with CBD:THC 1:1 and 6.9 with high-THC CBME. Similarly, nocturia episodes fell from 2.7 at baseline to 1.4 with the 1:1 mixture, and 1.5 with high-THC. Additionally, mean episodes of daily incontinence fell from a baseline of 2.1 to 1.0 with CBD:THC and 0.7 with high-THC CBME. These results will soon be published more formally.

In the past year, a small clinical trial of THC and a cannabis extract was performed with 16 subjects. Neither was observed to reduce spasticity, and adverse events were reported in the extract group (Killestein et al. 2002). Numerous criticisms were subsequently voiced in this regard (Russo 2003). Among these were that the plant extract was poorly categorized; in fact, it contained a fixed of THC to CBD with maximum doses of 5 mg of THC and 2 mg of CBD per day. The study additionally employed oral administration with no real dose titration. An additional study in Switzerland with more patients (57) and doses of up to 15 mg THC with 6 mg CBD divided tid has provided better results with reduction in spasms to the $p < 0.05$ level and no significant side effects vs. placebo (Vaney et al. 2002). A study of an even larger cohort in the UK is pending publication.

The results of a Phase II study of CBME have recently been published (Wade et al. 2003). This clinical trial was performed in Oxford, England with 24 subjects with treatment-resistant MS, spinal or brachial plexus injury comparing THC, CBD, THC:CBD, and placebo sublingual extracts employing consecutive series of double-blind, randomized, placebo-controlled single patient cross-over trials. Subjective and objective measures of pain, spasticity, spasm et al. were monitored along with adverse effects. Results were monitored employing subjective and objective blinded ratings and visual analogue scales (VAS). Twenty of the subjects completed the trial. Results with statistical significance included:

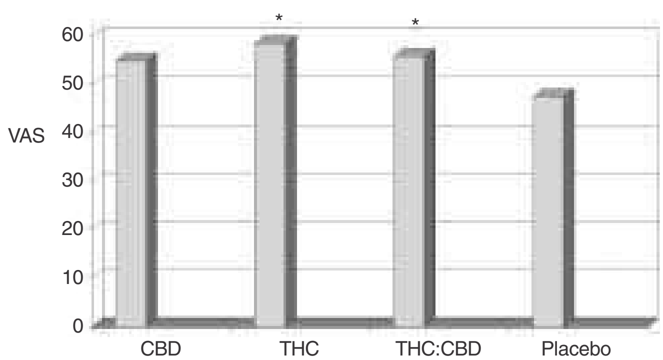
1. Pain scores were improved with both high-THC and high-CBD CBME vs. placebo ($p < 0.05$) (Figure 1).
2. Spasm was improved with both the high-THC and fixed-ratio THC:CBD CBME ($p < 0.05$) (Figure 2).
3. Similarly, spasticity was improved subjectively with the high-THC preparation ($p < 0.05$) (Figure 3).
4. As might be surmised, the high-THC CBME improved subjective measure of appetite ($p < 0.05$) (Figure 4).
5. The fixed-ratio THC:CBD CBME produced the best improvement in subjective sleep ($p < 0.05$) (Figure 5).
6. Turning to blinded objective measures, all three extracts, high-THC, high-CBD and fixed-ratio THC:CBD CBME improved spasticity on a numerical symptom scale ($p < 0.05$) (Figure 6).
7. Similarly, the high-THC and THC:CBD fixed-ratio CBME's yielded statistically significant objective improvement in spasm frequency ($p < 0.05$) (Figure 7).

FIGURE 1. Pain Improvement, N = 20, Daily VAS



* = $p < 0.05$
Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

FIGURE 2. Spasm, N = 20, Daily VAS

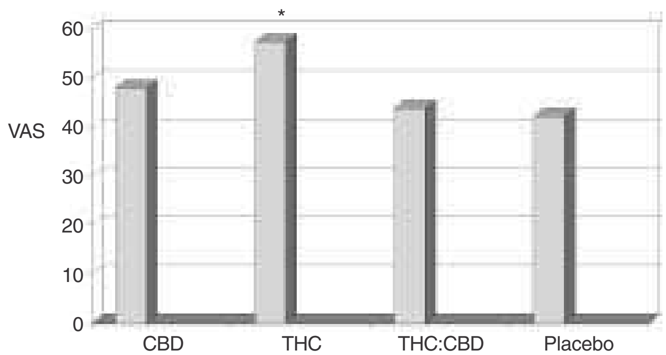


* = $p < 0.05$
Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

Adverse effects in the trial were predictable and well tolerated.

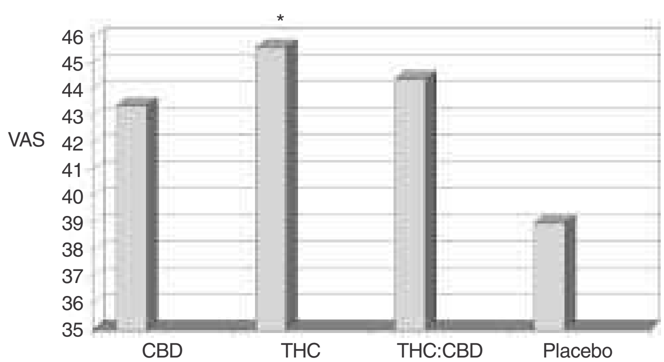
Additional Phase II work has been pursued in chronic pain patients intractable to conventional pharmacotherapy by the team of Notcutt et al. at James Paget Hospital in Great Yarmouth, UK. This work is pending more formal publication, but has been reported in 9 abstracts in the *Journal of Cannabis Therapeutics* from the 2001 meeting of the International Association for Cannabis as Medicine in Berlin (Notcutt 2002; Notcutt et al. 2002, 2002, 2002, 2002, 2002, 2002, 2002, 2002), as well

FIGURE 3. Spasticity, N = 20, Daily VAS



* = $p < 0.05$
Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

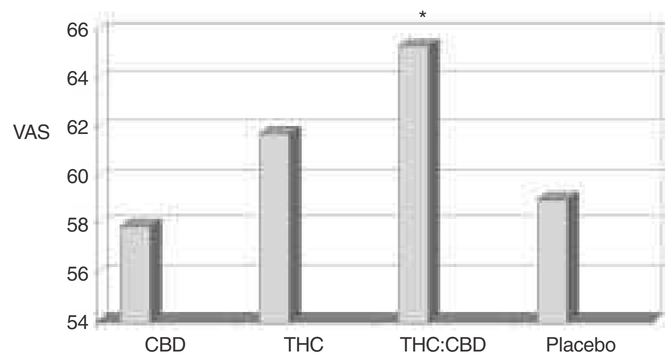
FIGURE 4. Appetite, N = 20, Daily VAS



* = $p < 0.05$
Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

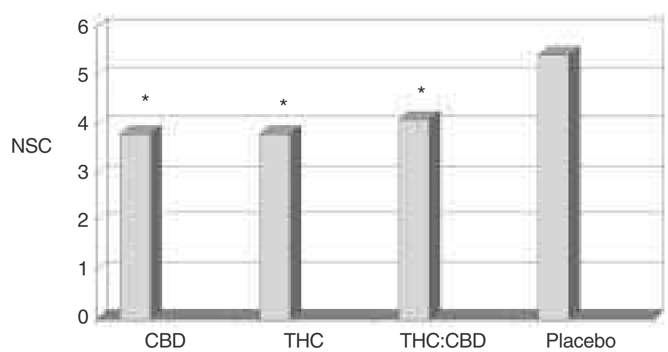
as the 2002 meeting of the International Cannabinoid Research Society in Asilomar, California (Notcutt 2003). Briefly stated, 34 N-of-1 studies were performed in a cohort of inadequately controlled pain patients, including those with MS (16), chronic back pain and sciatica (eight), other neuropathic pain (five), complex regional pain syndrome (CRPS, or "reflex sympathetic dystrophy") (two), and polyarthralgia, stiff man syndrome and myopathy (one each). Subjects included both cannabis-experienced and cannabis-naïve individuals. After a two-week base-

FIGURE 5. Sleep, N = 20, Daily VAS



* = $p < 0.05$
Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

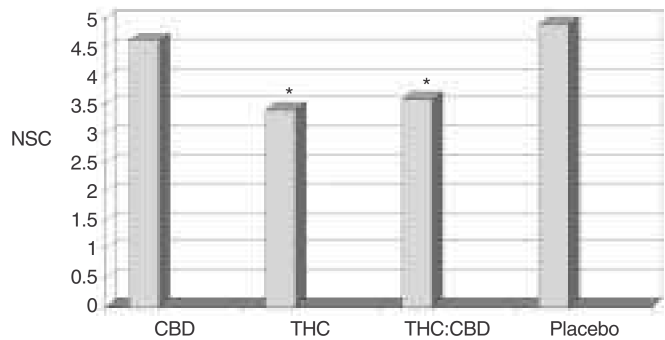
FIGURE 6. Spasticity Severity, Numerical Symptom Scale, N = 20, Observer Rated



* = $p < 0.05$
Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

line evaluation, a subsequent two-week open-label titration trial (one spray every 30 minutes to a limit of four with subsequent patient-directed upward titration) was pursued with fixed-ratio THC:CBD, followed by two separate four-week double-blind randomized trials of one week each of high-THC, high-CBD, fixed-ratio THC:CBD or placebo. General benefits were noted in CBME groups in pain, sleep, depression, activity and overall health compared to placebo. Interestingly, individ-

FIGURE 7. Spasm Frequency, Numerical Symptom Scale, N = 20, Observer Rated



* = $p < 0.05$
Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

ual dose requirements varied tremendously in the cohort, with symptomatic control requiring 5-80 mg per day of THC, CBD or the mixture. Seven patients experienced substantial improvement with CBME over best available conventional treatment, while 13 (32.8%) had moderate benefit, eight (23.5%) had "some" benefit, and six (17.6%) had none. Some dysphoria occurred at dose initiation, particularly in cannabis-naïve patients, but passed in 2-3 hours. Postural hypotension occurred in three patients with dose overload, while lesser adverse effects included mucosal stinging, staining of teeth, taste change and dry skin. Randomization was broken in four patients, one was removed due to distress, one continued single-blind after marital issues, one continued after an orthostatic hypotension event, and one continued single-blind after a gastroenteritis, deemed unrelated. Overall, the CBME was felt to be effective and acceptable to patients. Twenty-nine patients (85%) elected to continue into a long-term safety study. In the aftermath of this study, subjects were noted to be able to engage in many high level pursuits of which they were previously incapable.

In November 2002, preliminary results from four Phase III randomized, double-blind, placebo controlled Phase III clinical trials in the UK with 350 patients were released by GW Pharmaceuticals, and are available online: <http://www.gwpharm.com/news_pres_05_nov_02.html>. Results from these studies included highly statistically significant reductions in neuropathic pain, spasticity and sleep disturbance. The topics of the studies included the following:

1. Neuropathic pain in MS
2. Pain and sleep disturbance in MS and other neurological conditions
3. Multiple symptoms in MS
4. Neuropathic pain in brachial plexus injury

In the Phase III study of neuropathic pain in multiple sclerosis, 66 patients were studied in double-blind parallel groups with THC:CBD vs. placebo. Pain relief with THC:CBD CBME was greater than placebo ($p < 0.01$), and sleep disturbance was relieved to the same level ($p < 0.01$).

In the Phase III chronic refractory pain trial, 70 subjects with MS and other conditions were examined in double-blind parallel groups with THC:CBD CBME. Pain relief was observed with decreased usage of rescue medication as compared to placebo ($p < .05$), and sleep disturbance was also diminished ($p < .05$).

A larger cohort of 160 MS patients was studied in a third double-blind parallel group examining the fixed-ratio THC:CBD CBME. Spasticity was improved to a highly statistically significant degree ($p < 0.01$), while trends of improvement were also noted for a variety of other associated symptoms.

Finally, a fourth study examined brachial plexus injury, an intractable pain syndrome most often encountered after motorcycle accidents in the UK. In the largest study and first ever controlled clinical trial in this disorder, 48 subjects were studied in a double-blind crossover protocol comparing THC, THC:CBD and placebo. THC and THC:CBD CBME both reduced pain greater than placebo to a highly statistically significant degree ($p < 0.01$). THC and THC:CBD CBME both reduced sleep disturbance to a significant degree ($p < 0.05$).

Certain other features of the trials deserve emphasis. Firstly, after 350 patient-years of experience with CBME, the improvements in clinical parameters involved were attained above and beyond those achievable with best-available "conventional" pharmaceuticals. Additionally, with self-titration, most patients were capable of alleviating their symptomatology without adverse effects on activities of daily living (ADL). The safety profile was judged, "excellent."

At the time of this writing (May 2003), five additional Phase III clinical trials including cancer pain and spinal cord injury are in process, and will be completed in 2003, at which time a cumulative 1000 patients shall have been studied.

Finally, a team in Germany has recently published a Phase II study of oral THC in Tourette syndrome (TS) (Muller-Vahl, Schneider et al. 2003), in which 24 patients were treated over 6 weeks with up to 10 mg a day in a randomized, double-blind, placebo-controlled study. Tics were assessed by a variety of measures both subjectively and objectively. Seven patients dropped out, but only one due to adverse effects. Significant benefits were noted ($p < 0.05$) in a variety of measures with no serious adverse effects. The authors concluded that THC was safe and effective in treatment of tics associated with Tourette syndrome.

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Future of Cannabis and Cannabinoids in Therapeutics

Ethan Russo

SUMMARY. This study reviews human clinical experience to date with several synthetic cannabinoids, including nabilone, levonantradol, ajulemic acid (CT3), dexanabinol (HU-211), HU-308, and SR141716 (Rimonabant®). Additionally, the concept of "clinical endogenous cannabinoid deficiency" is explored as a possible factor in migraine, idiopathic bowel disease, fibromyalgia and other clinical pain states. The concept of analgesic synergy of cannabinoids and opioids is addressed. A cannabinoid-mediated improvement in night vision at the retinal level is discussed, as well as its potential application to treatment of retinitis pigmentosa and other conditions. Additionally noted is the role of cannabinoid treatment in neuroprotection and its application to closed head injury, cerebrovascular accidents, and CNS degenerative diseases including Alzheimer, Huntington, Parkinson diseases and ALS.

Excellent clinical results employing cannabis based medicine extracts (CBME) in spasticity and spasms of MS suggests extension of such treatment to other spasmodic and dystonic conditions.

Finally, controversial areas of cannabinoid treatment in obstetrics, gynecology and pediatrics are addressed along with a rationale for such interventions. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com> © 2003 by The Haworth Press, Inc. All rights reserved.]*

Ethan Russo, MD, is a Clinical Child and Adult Neurologist, Clinical Assistant Professor of Medicine, University of Washington, and Adjunct Associate Professor of Pharmacy, University of Montana, 2235 Wylie Avenue, Missoula, MT 59802 USA (E-mail: erusso@montanadsl.net).

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KEYWORDS. Nabilone, levonantradol, ajulemic acid, dexanabinol, HU-308, SR141716, cannabis, medical marijuana, migraine, idiopathic bowel disease, fibromyalgia, night vision, retinitis pigmentosa, neuroprotection, dystonia, obstetrics, gynecology, pediatrics

INTRODUCTION

As is evident from preceding information in this publication, an increasingly bright future seems to be on the horizon for cannabis therapeutics, whether herbally-based or designed to utilize its various components. The pros and cons of cannabis proper, whether smoked, ingested orally, or vaporized have been previously addressed. A wide variety of delivery systems is possible in the future. The present selection will detail additional preparations, particularly synthetic cannabinoids, and discuss how they and cannabis-based pharmaceuticals may be applied in future clinical therapeutics.

NABILONE

Nabilone is a synthetic cannabinoid, pharmacologically similar to THC, but with higher potency, a lesser likelihood to produce euphoria, and displaying a lower "abuse potential" (Association 1997). It is manufactured by Eli Lilly Company as Cesamet® and is available in the UK, Australia, Canada, and some European nations (Grotenhermen 2001), where it is primarily utilized as an anti-nausea agent in chemotherapy. Occasional reports have claimed benefit on spasticity in multiple sclerosis and dyskinesias. Lethal reactions have occurred in chronic canine usage (Mechoulam and Feigenbaum 1987).

Analgesic effects of nabilone in neuropathic pain patients have been noted (Notcutt, Price, and Chapman 1997), but prominent adverse effects included drowsiness and dysphoria. Some patients stated a clear preference for smoked cannabis in terms of side effects and analgesic efficacy. Nabilone's cost was estimated to be 10 times higher than herbal cannabis at black market rates, and all things considered, this agent would seem to have more disadvantages in the long term.

LEVONANTRADOL

Levonantradol is another synthetic cannabinoid from Pfizer. Analgesic benefits of up to 6 hours were noted in post-operative pain patients in

a prior trial (Jain et al. 1981), but without clear dose-response effects. Adverse effects are prominent with this agent, including somnolence in 50-100% and dysphoria in 30-50% (Association 1997), termed "unacceptable" by that authority.

AJULEMIC ACID (CT3)

Ajulemic acid is a synthetic cannabinoid derived from the more stable THC-11-oic acid that does not bind to CB_1 receptors and lacks psychoactive effects. It is currently in commercial development. It has shown strong analgesic and anti-inflammatory properties in animal models of arthritis without COX-1 inhibition side effects such as ulcer production, and is advanced clinical trials (Burstein 2001, 2000). It shares anti-neoplastic effects with THC on a variety of cell lines (Recht et al. 2001), but is half as potent in this regard, although longer acting. Ajulemic acid has recently been demonstrated to bind to the peroxisome proliferator-activated receptor gamma, part of the nuclear receptor superfamily involved in inflammatory processes (Liu et al. 2003), and also to suppress human monocyte interleukin-1beta production *in vitro* (Zurier et al. 2003). Ajulemic acid portends to be a valuable addition to the pantheon of cannabinoid pharmaceuticals employed for analgesic and anti-inflammatory properties.

DEXANABINOL (HU-211)

Dexanabinol is a synthetic cannabinoid agent developed at Hebrew University from Δ^8-THC, but it is a non-psychoactive enantiomer of the fabulously potent HU-210 (Pop 2000). It has demonstrated numerous interesting properties including antioxidant and anti-inflammatory effects, as well as suppression of THF-alpha (tumor necrosis factor) production. Additionally, it reduced brain damage associated with soman (Sarin)-induced seizures in rats (Filbert et al. 1999), caused reduction of experimental autoimmune encephalomyelitis responses (Achiron et al. 2000) suggesting application in multiple sclerosis, and reduced damage in experimental focal ischemia (Lavie et al. 2001). Human trials have demonstrated mixed results. In one such Phase II study of 67 closed head injury patients, dexanabinol reduced intracranial pressure and perfusion significantly with a good adverse effect profile (Knoller et al.

2002), with some degree of improvement in clinical outcome scales after 3 and 6 months.

Dexanabinol is currently in Phase III clinical trials, and further analysis will demonstrate its relative place in the cannabinoid pharmacopoeia. As currently formulated, parenteral injection of dexanabinol is required, and it may not possess the multi-modality efficacy of Cannabis Based Medicine Extracts.

HU-308

Another agent emerging from the research of Raphael Mechoulam's laboratories in Israel is HU-308, a synthetic and specific CB_2 agonist lacking cannabinoid behavioral effects in laboratory animals (Hanus et al. 1999). Observed activities of this agent include inhibition of forskolin-stimulated cyclic AMP production, blood pressure reduction, inhibition of defecation, and production of peripheral analgesia with anti-inflammatory effects. Further testing may demonstrate an important therapeutic role for this agent.

SR141716 (RIMONABANT®)

Heretofore, our discussion has centered on cannabinoid agonists or analogues. However, given the profile of cannabinoid stimulation with its decremental effects on short-term memory acquisition and stimulation of hunger, it was expected that efforts would be mounted to clinically harness antagonistic cannabinoid effects. SR141716, dubbed Rimonabant®, is a potent CB_1-antagonist or inverse agonist used extensively in laboratory studies. It has demonstrated anti-obesity effects in mice (Ravinet Trillou et al. 2003), and is currently in human clinical trials. Preliminary results (Le Fur et al. 2001) demonstrate reduction of hunger and food intake in obese male subjects in the short term, and weight reduction in the long term, with a reportedly benign adverse effect profile. Certainly, caveats are necessary, and one might expect the emergence of depression and hyperalgesic states in patients taking this agent, such as migraine and fibromyalgia. Additionally, hypervigilance will be necessary in administering such a drug to women of child-bearing age, as SR141716 has profound effects on neonatal feeding and growth (Fride 2002).

NEW INDICATIONS FOR CANNABINOID PHARMACEUTICALS

Emerging concepts have demonstrated the key role that endocannabinoids play in regulation of pain (Pertwee 2001), hormonal regulation and fertility (Bari et al. 2002), hunger (Fride 2002) and gastrointestinal function (Pertwee 2001), and even regulation of memory (Hampson and Deadwyler 2000), and proper extinction of aversive events (Marsicano et al. 2002).

Some of these concepts have recently been reviewed (Baker et al. 2003). In particular, the authors distinguish that cannabis and endocannabinoids may demonstrate an impairment threshold if too elevated, a range of normal function below which a deficit threshold is breached. This seems to be a simple and universal concept: for every neurotransmitter or neuromodulatory agent, there may be too much or too little, with corresponding clinical pathophysiological sequelae. With respect to endocannabinoids, this concept has been insufficiently explored. Previously, this author has postulated the likelihood of clinical endogenous cannabinoid deficiency diseases (CECDD) (Russo 2001, 2001), including migraine, fibromyalgia, idiopathic bowel syndrome (IBS, "spastic colon") and possible even psychiatric conditions, such as obsessive-compulsive disorder. In light of newer information, one may posit the addition of many other disease conditions that are seemingly unresponsive to pharmacotherapy with other agents that do not influence the endocannabinoid system: causalgia and allodynia as in brachial plexus neuropathy and phantom limb pain, post-traumatic stress disorder (PTSD), bipolar disease (Grinspoon and Bakalar 1998), dysmenorrhea (Russo 2002), hyperemesis gravidarum (Russo 2002; Curry 2002), unexplained fetal wastage, glaucoma (Jarvinen, Pate, and Laine 2002), and many others.

In the area of pain, it may be the case that we need to renew a therapeutic maneuver of the 19th century (reviewed in (Russo 2002), and supported in (Cichewicz and Welch 2002)) by combining cannabinoids and opioids, particularly post-operatively or in cases of major trauma, thereby producing analgesic synergy, reducing dosages, and adverse effect profiles with respect to opiate-induced nausea, constipation and dysphoria.

Recently, a new indication for cannabinoid manipulation has been claimed, that of improved night vision. Based on simultaneous ethnobotanical claims of fisherman that cannabis stimulated their ability to see in the dark (West 1991; Merzouki and Molero Mesa 1999) in Jamaica

and Morocco, respectively, a two-pronged pilot study was launched (Russo et al. 2003). In a double-blind controlled dosage escalation study with THC as Marinol®, improvement in scotopic sensitivity was noted in one subject, while in a subsequent field study with smoked *kif* (*Cannabis sativa/Nicotiana rustica* mixture) in three subjects, improvement in both dark adaptation and scotopic sensitivity thresholds were noted with the SST-1 Scotopic Sensitivity Tester (Peters, Locke, and Birch 2000). Given the relative paucity of CB_1 receptors in the striate cortex (Glass, Dragunow, and Faull 1997), and their particular density in rod spherules (Straiker et al. 1999), this phenomenon seems to be of retinal, rather than cortical origin. This is further supported by anecdotal claims that cannabis improves vision in retinitis pigmentosa (Arnold 1998). Based on these findings, more formal studies of RP with fully objective measures such as electroretinography seem warranted. Given the neuroprotective and antioxidant effects of cannabis and cannabinoids, extension of therapy to senile macular degeneration appears most promising.

CANNABINOIDS AND NEUROPROTECTION

In light of recent demonstration of the ability of THC and CBD to prevent cell death from glutamate toxicity (Hampson et al. 1998), a whole host of new therapeutic applications gain more than theoretical support beyond the current studies of stroke and closed head injury discussed in relation to dexanabinol. Therapeutic claims for cannabis in amyotrophic lateral sclerosis (ALS) have been advanced in a single case study (Carter and Rosen 2001), and it may prove to be that neurodegeneration may be diminished or arrested in this disorder, Huntington disease (Glass 2001), Parkinson disease (Sieradzan et al. 2001), Alzheimer disease (Volicer et al. 1997), and others. Neuroprotection is a valuable effect, as well, in treatment of seizure disorders (Cunha et al. 1980; Carlini and Cunha 1981; Wallace, Martin, and DeLorenzo 2002). The role of cannabis therapeutics in HIV encephalopathy and slow virus (prion) diseases (Bovine Spongiform Encephalopathy (BSE) or "mad cow disease," Creutzfeldt-Jakob disease, etc.) deserves exploration based on these preliminary findings.

Emerging concepts in psychiatry support that depression is not merely attributable to deficiencies of serotonin, norepinephrine or dopamine (Delgado and Moreno 1999), but rather, may represent a disorder of neuroplasticity suggesting the desirability to employ neuroprotective

agents. An extensive history of such use over the last 4000 years (Russo 2001), coupled with this new information, lends credence to the hypothesis. With their unique pharmacological profiles, CBMEs deserve an effort in clinical trials.

SPASMODIC DISORDERS

The current information supporting muscle relaxant benefits of cannabis and cannabinoids in MS and spinal cord injury is extremely compelling. Mining the data of the past (O'Shaughnessy 1838-1840; Christison 1851; Reynolds 1868, 1890), one may wonder anew about the role of cannabinoid therapeutics in disorders such as tetanus, hiccup (Gilson and Busalacchi 1998), stiff man syndrome, the various periodic paralyses, and dystonic disorders such as torticollis, dystonia musculorum deformans, stuttering, and writer's cramp.

FORBIDDEN TERRITORIES

Obstetrics and Gynecology

This topic has been recently reviewed at length (Russo 2002; Russo, Dreher, and Mathre 2003). Cannabis has been employed for millennia for a variety of related ills. Drugs are rightly eschewed when possible in pregnancy, but cases arise frequently wherein such treatment is necessary, even to save the life of mother and child. Close scrutiny of the literature supports the relative safety of cannabis in such applications, and particularly in episodic use, it is highly likely that the cost-benefit ratio in serious disorders is quite acceptable. Controlled studies of dysmenorrhea, hyperemesis gravidarum and other disorders with cannabis-extracts and medicines should be advanced.

Cannabinoid Medicines in Pediatrics

It is clear that cannabis and cannabinoids hold promise in for many intractable and desperate pediatric conditions, although this concept may be anathema to some.

Although it is frequently the butt of jokes, no one who has not been the parent of an affected infant can truly conceive of the stress and disturbance engendered by infantile colic. A developmental disorder ap-

pearing most often between two weeks and three months of life, this poorly understood syndrome produces nightly bouts of inconsolable crying and apparent abdominal cramping pain. Myriad remedies aimed at every imaginable neurotransmitter system of brain and gut tend to fail to stem its ravages. Perhaps infantile colic is another developmental clinical endogenous cannabinoid deficiency disorder. With its antispasmodic, analgesic, anti-anxiety and soporific attributes, a THC:CBD cannabis extract holds promise where other agents have disappointed, and if so, countless new parents may be thankful.

Another possible pediatric indication for cannabis-based medicines is cystic fibrosis. In a recent study (Fride 2002), an extremely compelling and well-conceived rationale for cannabis treatment was outlined that could vastly improve the clinical condition and well-being of affected children. Similar benefits might accrue to other serious failure-to-thrive states.

Cannabis medicines have already demonstrated remarkable success in allaying nausea and vomiting in children undergoing cancer chemotherapy (Abrahamov and Mechoulam 1995). Unfortunately, this study has been largely ignored, rather than being duplicated and extended. Any possible moral objection to such treatment holds no weight when the alternative is severe suffering and even death of a child. The recent report of cannabidiol (CBD) inhibition of glioma cell growth by promotion of apoptosis independent of cannabinoid and vanilloid receptor activity (Vaccani, Massi, and Parolaro 2003), should convince all but the most hardened detractors.

A less lethal, but yet still compelling potential indication is childhood asthma. The advent of new delivery devices for cannabis medicines discussed in this volume, combining bronchodilation, with modulation of leukotrienes and other mediators of inflammation offer unique benefits to this disorder.

Finally, the area of child psychiatry deserves additional consideration. A recent book, *Jeffrey's Journey: A Determined Mother's Battle for Medical Marijuana for Her Son* (Jeffries and Jeffries 2003), documents the case study of a young man who failed every conceivable psychopharmacological agent to control his anger and other psychopathology. Only oral cannabis worked, preventing his imminent institutionalization, and allowing a return to a semblance of normal life.

This author, in his practice of child and adult neurology, has heard dozens of unsolicited testimonials to the benefits of cannabis in attention-deficit hyperactivity disorder (ADHD), supporting available anecdotal accounts (Grinspoon and Bakalar 1997). Although the idea of

using cannabis-based medicines for this indication may seem surprising to most experts, controlled trials of cannabis medicines for children with ADHD seem clearly indicated, particularly in view of the controversies and side effects of existing psychotropic medications. Extension of the concept to other difficult disorders of obscure pathophysiology such as autistic spectrum and Asperger disorders may be warranted. If and when cannabis establishes its efficacy in pediatric diseases, it shall have achieved a fair measure of redemption from the derision it has elicited during the past century.

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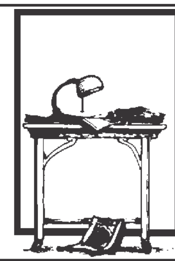
EDITORIAL



The *Journal of Cannabis Therapeutics* is proud to initiate its fourth year of publication with this issue, but regrets that it will be its last, as explained below.

In this final issue, we are pleased to present additional data on cannabinoid delivery and harm reduction. Dale Gieringer et al. present the first scientific analysis of results obtained with the Volcano®, a cannabis vaporizer device. The success of such technologies may address a key recommendation of the U.S. Institute of Medicine in its emphasis on non-smoked cannabis delivery systems.

Franjo Grotenhermen provides another extensive review article, this time on cannabinoid pharmacodynamics, to complement his previous offerings on cannabinoid pharmacokinetics.

Tod Mikuriya documents his extensive clinical experience in use of cannabis in treating alcoholism, an indication first claimed in the 19th century. Although sure to be controversial, this concept is one that deserves additional study considering the compelling public health issues and considerable cost to society. New approaches employing cannabinoid mechanisms may prove fruitful in providing alternatives to current treatment of this disorder

JOURNAL OF CANNABIS THERAPEUTICS: A REQUIEM

It is with great regret, but sense of pride, that we now "close the book" on this journal and allow it to stand on its previous offerings. This

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represents a decision that has been very difficult, but considered after extensive consultation with numerous editorial board members. I would like to outline the issues we have faced, the background of this decision, and review the accomplishments of the journal in its history.

A History of Our Goals

The *Journal of Cannabis Therapeutics* began as an idea advanced by Lester Grinspoon upon our first meeting in Washington, DC in November 1998. I immediately saw the logic of his concept: a place to publish the emerging abundance of information about clinical cannabis, the newly discovered endocannabinoid system that modulates so many vital physiological functions, as well as explore the clinical potential of synthetic cannabinoids. We envisioned a publication that would highlight the developing science, and hopefully serve as an educational resource for physicians and scientists, as well as interested members of the lay public.

I seized upon Lester's idea, and advanced it to my friend, mentor and editor of the Haworth Herbal Press, the late Dr. Varro (Tip) Tyler, who paid it and me the ultimate compliment, by saying that it was an idea whose time had come, but he would only support it if I were to be its Editor-in-Chief. Next to consult was Bill Cohen, the president and publisher of Haworth Press. He was wisely skeptical, but agreed to educate himself on the issue. To his surprise, the available information convinced him of the distinct advisability to proceed. Within three weeks, the idea became a concept. Bill's subsequent support has been unwavering.

Very quickly, a distinguished group of physicians and scientists agreed to take part as a core editorial advisory. A perusal of our contingent, 24 strong, reads as a "Who's Who" of influential authorities and authors in the area. Again, many voiced doubts, but agreed to lend their support. To their great credit, there have been no defections from their ranks in the life of the journal.

From the beginning, I set a number of goals. I felt from the onset that the journal should establish itself or cease publication after three years. We have just crossed that threshold, but barely. I naively thought at the time that *JCANT* might be rendered superfluous within this time-frame by a widespread acceptance of the concept of clinical cannabis. That, obviously, will take a little longer.

A key benchmark I set was for building a subscriber base of 1,000 or more. Another was acceptance of the journal in major university librar-

ies. Finally, was the gold standard: we sought recognition by Index Medicus for that critical accolade of acceptance for listing in that publication and the National Library of Medicine database.

We also wanted to be a home for expansive concepts and discussions on the topics of cannabis and cannabinoids–the kind of articles that would never gain acceptance in "mainstream" medical journals. Annual thematic double-issues would be co-published in book form.

Obstacles and Realities

After a year of planning, and gathering material, *JCANT*'s charter issue was released in early 2001, to critical surprise and reward. Subsequently, numerous copies were circulated at major meetings, to numerous compliments, including two letters of thanks from members of the US Supreme Court as they were considering the landmark Oakland Cannabis Buyers' Club case. I will treasure those.

Advance subscriptions were respectable in number, but despite the endorsements, rose but slowly over time. Our 2001 thematic issue became *Cannabis Therapeutics in HIV/AIDS*, which remains today the only book of its kind beyond the late Bob Randall's 1991 *Marijuana & AIDS*. More acclaim followed, but the subscriber numbers did not follow suit, nor approach our goal. North American physicians have been particularly slow to familiarize themselves with the new literature, and to attempt to understand what has motivated their patients to employ clinical cannabis, frequently without their knowledge or endorsement.

In 2002, we employed a generous grant from the Marijuana Policy Project to attempt to enter the realm of medical libraries. Free sample issues were offered to every such facility in the USA and Canada. Few actual subscriptions resulted. A reality of modern publishing is that such institutions have little shelf-space, and much sparser budgets for the new. Even the University of Montana asked me, "What current journal should be abandoned to make room for this offering?" Mass mailings were met with similar ennui.

The year was capped off with our second thematic issue, *Women and Cannabis: Medicine*, *Science and Sociology*, ably co-edited by Melanie Dreher and Mary Lynn Mathre. Once more, it was a unique offering on a previously taboo topic.

A similar scenario played out in 2003: critical acclaim and encouragement, but little advancement in subscriber base over a few hundred. Our initial application for Index Medicus recognition was turned aside negatively. The quest for double-blind controlled studies, the gold-stan-

dard of current medical proof, continued, but quite expectedly, the small numbers of available studies were placed in better-recognized large circulation publications. This is right and proper; the cannabinoid field has grown and matured dramatically since the inception of *JCANT* and these new concepts deserve immediate attention by professionals and medical consumers. I endorse the decision by the authors of these articles to seek wider recognition of their work, as is currently taking place with vaporizer research pioneered by Dale Gieringer with support from MAPS.

The 2003 volume was completed with our last thematic issue: *Cannabis: From Pariah to Prescription*, that documents the current state of the art with respect to phytocannabinoids, endogenous and synthetic cannabinoids, and advances our knowledge thereof as the first products approach marketing and acceptance in Europe.

By this time, a critical juncture was reached. Although the threshold of prescription clinical cannabinoids as a reality was nearing, the available pool of articles that would advance the knowledge and might lead to greater recognition has diminished. Prospects for additional database listing seem less than promising, and subscriber numbers have not risen despite additional grants-in-aid.

A Personal Note

I am experiencing some major life transitions at this time: moving our household and leaving neurology practice after 20 years to accept a position as Senior Medical Advisor to GW Pharmaceuticals. I had voiced my personal concerns about possible conflicts of interest with the publisher and numerous editorial board members, and was most pleased with their reassurances and vote of confidence. That, ultimately, has had no bearing on the decision to cease publication at a time when *JCANT* has maintained its quality on a consistent basis, rather than witness its possible diminution over time.

Our Accomplishments

I believe that the *Journal of Cannabis Therapeutics* has, in its short sojourn, advanced knowledge and acceptance of this emerging field. We have gained notice beyond the apparent subscriber numbers. Although *JCANT* may not have influenced the Supreme Court to accept clinical cannabis, our articles have been cited in major national commissions, including *A Report of the National Commission on Ganja* in

Jamaica in 2001 (*http://www.drugtext.org/library/reports/ganjamaica.htm*), and even more prominently in *Cannabis: Our Position for a Canadian Public Policy*, the report of the Canadian Senate in 2002 (*http://www.parl.gc.ca/Common/Committee_SenRecentReps.asp?Language=E&Parl=37&Ses=1*). Both commissions strongly endorsed greater public access to clinical cannabis.

I was very pleased that our lead article of volume 1, number 1, was a review of the current state of cannabis therapeutics as conceived by Leo Hollister, the American dean of scientific study of the herb, but was saddened that it came to be his final publication. Another landmark of the inaugural edition was the study of Musty and Rossi describing the success of smoked cannabis in allaying nausea in several hundred subjects in state-sponsored studies of previous decades that had never before been published (for both, see link to *JCANT* 1(1) below).

Innovative articles on therapeutic possibilities of cannabis and cannabinoids followed, including music appreciation, an examination of ancient and ethnobotanical evidence, and many more. Surveys of clinical cannabis use in various countries were offered, as well as closer examinations of non-cannabinoid components, endogenous cannabinoids, and novel delivery systems. Volume 2 saw the publication of the "Chronic Use Study" in which, for the first time, information was made available concerning the benefits and side effects of cannabis for a small cohort of legal patients in the US Compassionate Use Investigational New Drug Program (see link below). This study has had an influence far beyond the subscriber base, and has led to many associated news stories and publicity about the issues.

Further evolutionary ideas concerning cannabis were provided by many authors. Volume 3 continued in a similar vein, with more information on use surveys, vaporization technology, pharmacokinetics, and the advent of cannabis-based medicine extracts and oro-mucosal delivery.

THE FUTURE

I envision that the fields of cannabis and cannabinoid therapeutics will flourish in the coming decade as our understanding of the key role of endogenous mechanisms unfolds, and governments slowly accept the wisdom that these medicines can play a major role in alleviating human suffering from legion complaints. The advancement of that concept should properly occur in venues with greatest accessibility and

visibility, and I will be working toward that goal. I hope and expect to continue to publish review material in book form with the continued largesse and support of The Haworth Press.

Franjo Grotenhermen, the founder and president of the International Association of Cannabis as Medicine, has graciously agreed to expand the *IACM-Bulletin* (*http://www.acmed.org/english/home.htm*) so that topical reviews and new ideas that might not see publication in mainstream sources will have an outlet.

We will make further efforts to ensure that the useful legacies of the *Journal of Cannabis Therapeutics* will endure and be accessible. Currently, portions of the content are available online:

- Charter Issue, *Journal of Cannabis Therapeutics* 1(1), 2001 (*http://www.cannabis-med.org/jcant/Jcant(1).pdf*)
- *Journal of Cannabis Therapeutics* articles by Ethan Russo:
- Hemp for Headache (*http:///www.cannabis-med.org/jcant/Jcant1(1).pdf*)
- McPartland/Russo: Cannabis and Cannabis Extracts: Greater than the Sum of Their Parts? (*http://www.montananorml.org/docs/McPartland-Russo-JCANT-1-3-4-2001.pdf*)
- Chronic Use Study (*http://www.cannabis-med.org/jcant/russo_chronic_use.pdf*)
- Cannabis in OB/GYN (*http://www.freedomtoexhale.com/russo-ob.pdf*)

We will secure additional availability of *Journal of Cannabis Therapeutics* content at intervals after publication as time progresses. Eventually, we would essay to have the entire body of the work available electronically to all interested people.

In closing, I would like to thank Lester for his idea, Tip for his support that has sustained me beyond his passing, Bill for his enduring encouragement, Dale Gieringer, Franjo Grotenhermen, John McPartland for their multitudinous submissions, GW Pharmaceuticals for their commitment to the future of cannabinoid therapeutics, and all the remaining board members and subscribers for their attention and largesse. For this, I am extremely grateful.

Ethan Russo, MD
Editor

Cannabis Vaporizer Combines Efficient Delivery of THC with Effective Suppression of Pyrolytic Compounds

Dale Gieringer
Joseph St. Laurent
Scott Goodrich

ABSTRACT. Cannabis vaporization is a technology designed to deliver inhaled cannabinoids while avoiding the respiratory hazards of smoking by heating cannabis to a temperature where therapeutically active cannabinoid vapors are produced, but below the point of combustion where noxious pyrolytic byproducts are formed.

This study was designed to evaluate the efficacy of an herbal vaporizer known as the Volcano®, produced by Storz & Bickel GmbH&Co. KG, Tuttlingen, Germany (http://www.storz-bickel.com). Three 200 mg samples of standard NIDA cannabis were vaporized at temperatures of 155°-218°C. For comparison, smoke from combusted samples was also tested.

The study consisted of two phases: (1) a quantitative analysis of the solid phase of the vapor using HPLC-DAD-MS (High Performance Liq-

Dale Gieringer is affiliated with California NORML, 2215-R Market Street #278, San Francisco, CA 94114.

Joseph St. Laurent and Scott Goodrich are affiliated with Chemic Labs, 480 Neponset Street, Building #7C, Canton, MA 02021.

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uid Chromatograph-Diode Array-Mass Spectrometry) to determine the amount of cannabinoids delivered; (2) a GC/MS (Gas Chromatograph/Mass Spectrometer) analysis of the gas phase to analyze the vapor for a wide range of toxins, focusing on pyrene and other polynuculear aromatic hydrocarbons (PAHs).

The HPLC analysis of the vapor found that the Volcano delivered 36%-61% of the THC in the sample, a delivery efficiency that compares favorably to that of marijuana cigarettes.

The GC/MS analysis showed that the gas phase of the vapor consisted overwhelmingly of cannabinoids, with trace amounts of three other compounds. In contrast, over 111 compounds were identified in the combusted smoke, including several known PAHs.

The results indicate that vaporization can deliver therapeutic doses of cannabinoids with a drastic reduction in pyrolytic smoke compounds. Vaporization therefore appears to be an attractive alternative to smoked marijuana for future medical cannabis studies.

KEYWORDS. Marijuana, cannabis, vaporization, smoking, harm reduction

INTRODUCTION

Concern about the respiratory hazards of smoking has spurred the development of vaporization as an alternative method of medical cannabis administration. Cannabis vaporization is a relatively new technology aimed at suppressing respiratory toxins by heating cannabis to a temperature where cannabinoid vapors form (typically around 180-190°C), but below the point of combustion where smoke and associated toxins are produced (near 230°C). The purpose of this is to permit the inhalation of medically active cannabinoids while avoiding noxious smoke compounds that pose respiratory hazards. Of particular concern are the carcinogenic polynuclear (or "polycyclic") aromatic hydrocarbons (PAHs), known byproducts of combustion that are thought to be a major culprit in smoking-related cancers. While there exists no epidemiological evidence that marijuana smokers face a higher risk of smoking-related cancers, studies have found that they do face a higher risk of bronchitis and respiratory infections (Polen et al. 1993, Tashkin 1993). This risk is not thought to be due to cannabinoids, but rather to extraneous byproducts of pyrolysis in the smoke.

In principle, vaporization offers medical cannabis patients the advantages of inhaled routes of administration: rapid onset, direct delivery into the bloodstream, ease of self-titration and concomitant avoidance of over- and under-dosage, while avoiding the respiratory disadvantages of smoking. Compared to other proposed non-smoked delivery systems using pharmaceutical extracts and synthetics, vaporization also offers the economic advantage of allowing patients to use inexpensive, homegrown cannabis.

In practice, the major question concerning vaporization comes down to feasibility. How well can one design a vaporizer that reliably produces "smokeless," toxin-free cannabinoid vapors from crude cannabis? To address this question, we tested a device known as the Volcano®, an herbal vaporizer produced by Storz & Bickel GmbH&Co. KG, Tuttlingen, Germany (http://www.storz-bickel.com). The study was designed to measure how efficiently the device delivered delta-9-tetrahydrocannabinol (THC) and other cannabinoids, and how effectively it suppressed other, non-cannabinoid compounds from the vapor.

The study consisted of two phases: (1) a quantitative analysis of the solid phase of the vapor using HPLC-DAD-MS (High Performance Liquid Chromatograph-Diode Array-Mass Spectrometry) to determine the amount of cannabinoids delivered; (2) a GC/MS (Gas Chromatograph/Mass Spectrometry) analysis of the gas phase to analyze the vapor for a wide range of toxins, focusing on pyrene and other polynuculear aromatic hydocarbons. Vapor was generated by loading the Volcano with 200 mg samples of NIDA cannabis. For comparison, a combusted control using 200 mg of cannabis burned in a glass pipe bowl was also tested.

Upon analysis, the Volcano vapors were found to consist overwhelmingly of cannabinoids, while the combusted control contained over one hundred additional chemicals, including several known PAHs. The results, which are discussed below, provide encouraging confirmation of the feasibility and efficacy of vaporization.

This study was the third in a series of cannabis smoke harm reduction studies sponsored by California NORML (National Organization for the Reform of Marijuana Laws, www.canorml.org) and MAPS (Multidisciplinary Association for Psychedelic Studies, www.maps.org) (Gieringer 2001). The first study tested a variety of smoking devices, including two crude homemade vaporizers along with several waterpipes and other devices, specifically examining THC and solid smoke tars (Gieringer 1996). It indicated that only vaporizers were capable of achieving reductions in tar relative to THC. The second study (Chemic 2000) was a

"proof of concept" study of an electric radiant heat vaporizer known as the M-1 Volatizer® (http://www.volatizer.com). The M-1 was found to deliver THC while completely eliminating three specific toxins (naphthalene, benzene and toluene) in the solid phase of the vapor. The study also detected a $\geq$ 56% reduction in tars and a qualitative reduction in carbon monoxide, but did not test for any other chemicals (Gieringer 2001). The present study (Chemic 2003) is the first to use a GC/MS to analyze the gas phase of vaporized cannabis for a wide range of toxins, concentrating on the highly carcinogenic PAHs.

DESCRIPTION OF THE VOLCANO®

The Volcano, as its name suggests, consists of a conical body containing a ceramic heater with a heat vent on top (Figure 1). Above the vent sits a removable chamber that is loaded with sample material. Hot air is blown from below through the sample to produce vapor, which is collected in a detachable plastic balloon. After the balloon has been filled, it can be removed and fitted with a mouthpiece, through which the vapors can be inhaled. The balloon is a unique feature of the Volcano. It has the advantages of preventing loss of sidestream vapor and providing a uniform, consistent dosage volume. This renders it an ideal instrument for controlled dosage studies.

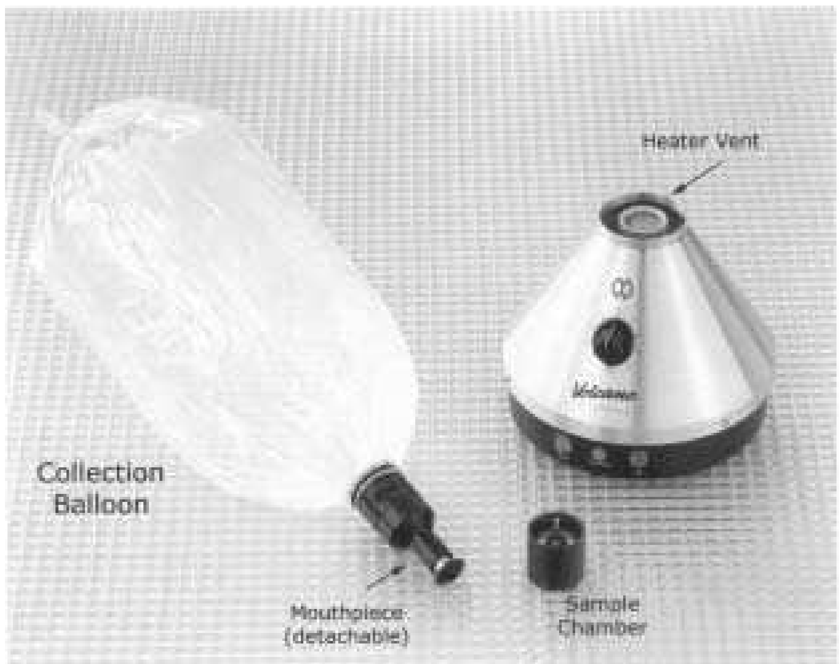
The temperature control ranges from 1 to 9, corresponding to temperatures of 130° to 226°C. The manufacturer suggests using a temperature setting of 7, corresponding to a nominal 202°C. Our previous study using the M-1® found that sample temperatures around 185°C were optimal for vaporization, with toxins beginning to appear above 200°C (Chemic 2000, Gieringer 2001). As a worst-case test of the Volcano's safety, we set it at its highest setting to ascertain whether pyrolytic byproducts might result. Two thermocouples were placed in the vaporizer above and below the sample to determine the actual operating temperature. The temperature was found to be stable, measuring 155°C on the top surface of the sample and 218°C on the screen closest to the heater.

THE SAMPLE

The sample consisted of standard NIDA cannabis supplied through an independent laboratory. Portions were prepared in 1.7 gram batches by gently sifting through a 2 mm sieve screen and mixing.

The baseline concentrations of cannabinoids in the sample were ana-

FIGURE 1. The Volcano® Vaporizer



Photograph courtesy of Storz & Bickel.

lyzed by Soxhlet extraction for THC, cannabidiol (CBD) and cannabinol (CBN). Three separate samples of 200 mg were extracted in 250 ml ethanol under heat for 2 hours, concentrated by rotary evaporation, and analyzed by HPLC-DAD-MS. The mean concentration of THC was 4.15% (range 4.0%-4.3%), consistent with NIDA standards. CBD and CBN were detected in only trace amounts, with the CBD showing a wide range of variance: 0.0428%-0.128% (mean 0.075%). CBN ranged more tightly from 0.086% to 0.10% (mean 0.094%).

The water content of the sample was measured by heating a prepared 0.56 gram sample for 30 minutes at 140°C and measuring the weight loss. The water content was found to be 11.9% by weight.

PHASE ONE: CANNABINOID RECOVERY ANALYSIS

Vapor from the Volcano was analyzed to determine the cannabinoid delivery efficiency of the vaporizer. A 200 mg sample was loaded into

the Volcano and exposed to heat for 45 seconds, enough to fill the collection balloon. The vapor was then transferred from the balloon over a period of approximately 15 minutes by a vacuum pump into a solvent reservoir containing 50 ml of methanol.

Three balloons were collected from each sample. The three balloon quota was based on preliminary tests, which found that most of the cannabinoids were delivered in the first two balloons, with just trace amounts in the third. The vapor is typically visible as a light gray wispy haze and has a distinct cannabis terpene odor. In practice, Volcano users report inhaling anywhere from two to six balloons from a given sample. However, most load the chamber with a half gram or more, over twice the sample size in our tests. The more cannabis that is loaded, the more balloons of vapor that can be drawn. According to the manufacturer, up to ten balloons can be drawn from a one-gram sample (Russo 2003). In order to facilitate maximal vaporization, the manufacturer recommends stirring the sample around after inhaling a few balloons, then repeating. However, this procedure was not followed in our tests since we used relatively small amounts of sieved material.

The dissolved vapor from the Volcano was subjected to quantitative analysis on the HPLC-DAD. Two separate samples of 1.5 ml were tested from each dissolved sample as a consistency check. The entire process was repeated for three different 200 mg samples of cannabis. Results are shown in Table 1. On average, the recovered THC amounted to 1.95% of the original weight of the sample, or 47% of the original THC in the crude sample. There was a large variance in the percentage of THC recovered in the three different vaporizer test runs, ranging from 36% to 61%. This suggests that the efficiency of vaporization is highly sensitive to variations in the sample and micro-conditions in its environment.

These results compare favorably to the delivery efficiencies of marijuana cigarettes as measured in other studies. THC efficiencies of 34% to 61% were reported in studies of marijuana cigarettes smoked via a smoking machine under varying conditions of puff duration and air speed (Fehr and Kalant 1971). Efficiencies of 50% were obtained using a machine designed to mimic human marijuana cigarette smoking (Manno 1970) and in an unpublished study at Battelle by Foltz et al. (cited in Truitt 1971). It has been estimated that 23-30% of the THC in combusted cannabis is destroyed by pyrolysis, while as much as 40-50% can be lost in sidestream smoke (Perez-Reyes 1990). Efficiencies as low as 16%-19% were reported in tests of cigarettes smoked intermit-

TABLE 1. Cannabinoid Recovery Efficiencies

(A) CRUDE CANNABIS (Soxhlet Extraction)

Sample	THC (%)	CBD (%)	CBN (%)
Crude 1	4.3	0.044	0.10
Crude 2	4.1	0.055	0.0925
Crude 3	4.0	0.127	0.0975
Mean (Std.Dev)	4.15 (0.17)	0.075 (0.044)	0.094 (0.007)

(B) VOLCANO VAPOR

Sample	THC (%)	CBD (%)	CBN (%)
Volcano 1	2.55	0.12	0.11
Volcano 2	1.50	0.068	0.0595
Volcano 3	1.80	0.081	0.070
Mean	1.95 (0.49)	0.091 (0.026)	0.081 (0.025)

(C) COMBUSTED SMOKE

Sample	THC (%)	CBD (%)	CBN (%)
Combustion 1	3.4	0.155	0.19
Combustion 2	3.2	0.16	0.185
Combustion 3	3.1	0.13	0.18
Mean	3.24 (0.11)	0.15 (0.016)	0.19 (0.005)

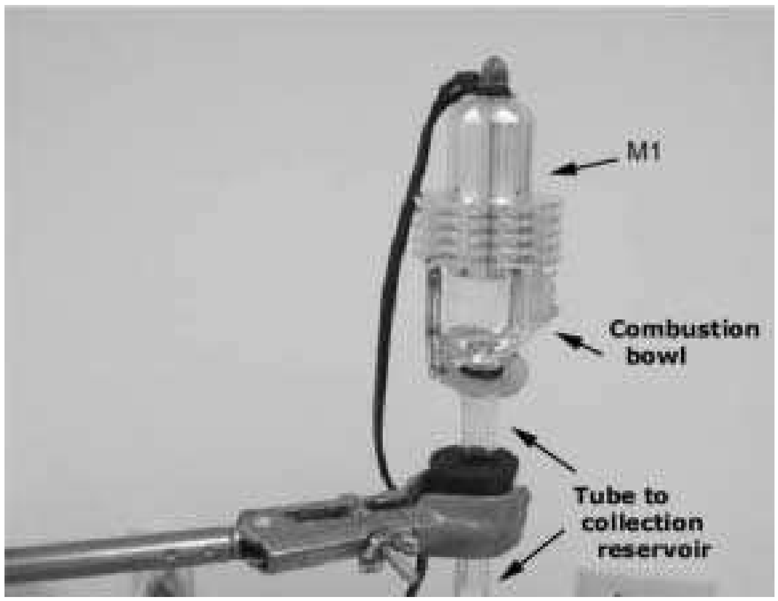
Note: Each sample was tested twice; in each case, results were consistent within 3%. Data above reflect the average of the two test results.

tently on smoking machines (Davis et al. 1984). In contrast, continuous smoking on a smoking machine yielded efficiencies of 69%.

The THC delivery of combusted cannabis was measured in our study by repeating the experiment with three more 200 mg samples. The samples were not rolled into cigarettes, but combusted in a glass pipe bowl like that of a marijuana bong. Each sample was ignited by exposure to an electric radiant heater placed over the bowl, and the smoke was drawn through a tube directly into the methanol (Figure 2). The dissolved smoke was assayed for cannabinoids as previously described.

The combusted sample registered a relatively high THC delivery efficiency of 78%. The variance was low for the three different test runs. The high efficiency may be explained by the fact that the laboratory conditions minimized loss of sidestream smoke; the sample was completely consumed with no "butt" remaining; and the pipestem led directly into the solvent so as not to cause excessive loss by adhesion to

FIGURE 2. Combustion Setup. Electric heater (MI) radiates down into bowl, igniting sample below. Smoke is drawn by vacuum through tube to solvent reservoir (below, not shown).



the walls. The amount of THC lost (22%) in combustion was consistent with the losses attributed to pyrolysis in other studies.

Theoretically, the vaporizer might have been expected to realize a higher THC delivery efficiency than combustion, since it should have avoided loss of THC by pyrolysis. That this was not observed indicates that there were other inefficiencies in the vaporization process. The most likely explanation would seem to be incomplete vaporization, due to lack of uniform thorough heating and ventilation of the sample. It is certainly possible that higher efficiencies might have been achieved by stirring the sample and drawing another balloon from the vaporizer, as recommended by the manufacturer.

All of the vaporized and combusted samples were also assayed for CBD and CBN. The amount of CBD delivered was unexpectedly somewhat higher for both the vaporized and combusted samples. At first glance, this result is not easy to explain. However, given the unusually high variance of CBD measured in the crude samples and the minimal levels of CBD detected, the results do not seem to be significant.

For CBN, there was no significant change under vaporization. In contrast, the level of CBN was twice as high in all three combusted samples, with little variance. This result may be explained by the oxidation of THC under heat (El Sohly 2002). However, it should be noted that the amounts of CBN observed were still quite low (0.19%), two orders of magnitude less than the loss of THC observed under combustion.

PHASE 2: GAS PHASE GC/MS ANALYSIS

The second phase of the study analyzed the gas phase of the vapor for a broad spectrum of compounds via GC/MS. The GC/MS was outfitted with a DB-XLB analytical separation column (DB-xtra low bleed, 30 M $\times$ 0.25 mm, 0.25 μm film), which is especially suited for the detection of polynuclear aromatic hydrocarbons.

A PAH reference stock solution was used that included analytes for naphthalene, acenaphthalene, anthracene, chrysense, benzo(a)pyrene, benzo(k)fluoranthene, 1,1,2-benzoperylene, indeno(1,2,3-c,d)pyrene, ancenaphthylene, fluorene, phenanthrene, pyrene, 1,2-benzanthracene, benzo(b)fluroanthene, and 1,2,4,6-dibenzanthrancene. Pyrene was used as a reference standard.

The evolved vapor from the Volcano was transferred from the collection balloon via vacuum directly to a 250 ml volatile gas trap. A 2.0 ml portion of the gaseous sample was then transferred using a headspace syringe directly onto the chromatographic system and assayed. In addition, the condensed residue that had adhered to the gas trap was analyzed by adding 2.0 ml of methanol to the trap to dissolve it. Subsequently, 1 μl of the solution was injected directly into the GC/MS. This process was repeated for three samples with three balloons from each sample, making a total of nine runs with gas samples and nine more with the condensed residue.

The gas was analyzed qualitatively and semi-quantitatively for polynuclear aromatic hydrocarbons at sample concentrations of 2.25-125 μg/ml. The GC/MS operated at a thermal gradient of 110°-320°C over 53 min. Different compounds were qualitatively identified by comparing their response peaks with an NBS reference library. Compounds that demonstrated greater than 70% match quality in comparison to the NBS mass spectral standard were reported as identified isolated compounds. Their mass concentrations were estimated from the response peak area in terms of the calibrated reference standard for pyrene. This yielded approximate, semi-quantitative mass determinations.

A review of the data showed that the Volcano vapor was overwhelmingly dominated by THC, with trace amounts of a handful of other compounds.

Representative data for the vapor gas and solvated condensate are shown in Tables 2 and 3 (from the first balloon of one of the samples).

Aside from THC, one other cannabinoid, CBN, was detected. No CBD was detected. This was not unexpected, since the GC/MS analysis was much less sensitive to cannabinoids than to PAHs. In general, the

TABLE 2. GC-MS Semi-Quantitative Results: Gaseous Headspace Analysis; Vaporized Sample

Retention time (min)	Response (area)	Best match	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
9.33	1221726	Caryophyllene[1]	78	0.0010	1.3
30.62	2417494	2-Methyl-2, 4 (2H-1-benzopyran-5-ol)	81	0.0020	2.5
32.56	85295887	Dronabinol (THC)	99	0.070	89.1
33.62	5487650	Cannabinol (CBN)	81	0.0045	5.7
42.97	1289703	5-[(Acetyl benz [e] azulene-3,8-dione	86	0.0011	1.3

Total recovered mass
as Pyrene (mg): 0.079**
Weight extracted (mg): 200
% recovered: 0.04**
** (Nominal semi-quantitative figures)

[1] "Sesquiterpinoid essential oil commonly found in cannabis." Ethan Russo, MD, Montana Neurobehavioral Specialists, Missoula, MT 59802.

TABLE 3. GC/MS Semi-Quantitative Results: Solvated Extract Analysis; Vaporized Sample

Retention time (min)	Response (area)	Best match	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
30.62	4961669	2-Methyl-2, 4 (2H-1-benzopyran-5-ol)	81	0.065	1.90
32.55	246510987	Dronabinol (THC)	99	3.2	94.3
33.62	9875017	Cannabinol (CBN)	94	0.13	3.78

Total recovered mass
as Pyrene (mg): 3.4**
Weight extracted (mg): 200
% recovered: 1.7**
** (Nominal semi-quantitative figures)

GC/MS analysis was intended to measure PAHs but did not provide an accurate measure of cannabinoids. For the latter, it was necessary to use the HPLC.

Aside from the cannabinoids, only three other compounds were tentatively identified in the vapor gas, and one in the solvated condensate. The three were caryophyllene (an aromatic terpene found in cannabis and other plants) plus two other compounds of undetermined origin, one of which also appeared in the condensate.

An estimated 1.7% of the weight of the 200 mg sample was recovered in the solvated condensate, as approximately quantified in terms of the pyrene standard. THC accounted for a nominal 94.3% of the inferred estimated mass. That the apparent concentration of THC inferred in the GC/MS analysis (3.2 mg/gm) was much lower than in the HPLC (19.5 mg/gm), was partly an artifact of the mathematical representation of THC in terms of pyrene, and partly due to the lack of applicability of the GC/MS system to THC due to low volatility and to sorbation characteristics of the analytic column.

The gaseous headspace was more tenuous, yielding an estimated recovered mass of just 0.04% of the sample weight. Once again, the sample was overwhelmingly dominated by THC.

A striking result in both analyses was a lack of significant quantities of pyrolytic-induced analytes in the vapor.

Comparison runs using combusted cannabis presented a strikingly different picture. As in the previous experiment, smoke produced by 200 mg of cannabis combusted under the M-1 was drawn into a 250 ml volatile gas trap. A 2 ml gaseous sample was injected into the GC/MS; 2.0 ml of methanol was added to the trap to dissolve the condensed, and another 1 μl sample was injected into the GC/MS for a second analysis. This process was repeated for three separate samples.

Representative results for the gas and solvated condensate are presented in Tables 4 and 5, respectively (data taken from first run).

Review of the data from the gaseous headspace detected 111 tentatively identified compounds, including THC and CBN. Included were five known PAHs. Cannabinoids represented only 12% of the inferred recovered mass; the remaining 88% consisted of extraneous products of combustion.

The solvated extract yielded 37 tentatively identified compounds, including five known PAHs. THC and CBN constituted 90% of the estimated recovered mass. (When combusted, the product saturated the chromatographic system, producing a distorted response; hence the apparently elevated concentration of THC (57.9 mg/gm); as noted above,

TABLE 4. GC/MS Semi-Quantitative Results: Gaseous Headspace Analysis; Combusted Sample

Retention time (min)	Response (area)	Best match[1]	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
4.30	32935726	Benzeneacetonitrile	91	0.027	0.16
4.60	2310571	1-Chloro-octadecane	91	0.002	0.01
4.99	18390657	Naphthalene	90	0.015	0.09
5.18*	69332076	2,3-Dihydro-benzofuran	86	0.057	0.34
6.21	4465468	2,6,10,14-Tetramethyl-hexadecane	90	0.004	0.02
6.91	86166759	Indole	90	0.071	0.42
7.12	7925421	1-Methyl-naphthalene	93	0.007	0.04
8.52	35115397	1,1′-Oxybis-octane	83	0.029	0.17
8.69	12256513	2,6,10-Trimethyl-tetradecane	83	0.010	0.06
9.00	23982131	3-Methyl-1H-indole	81	0.020	0.12
9.32	116897251	Caryophyllene	98	0.096	0.57
10.15	313228545	Cyclododecane	97	0.257	1.52
10.74	4799627	Pentadecane	97	0.004	0.02
10.85	146804387	Heptadecane	98	0.120	0.71
11.35	950013208	Nonadecene	86	0.780	4.60
11.95*	90056152	2,2′-Diethyl-1,1′-biphenyl	94	0.074	0.44
12.63	154063760	Hexadecanal	76	0.126	0.75
13.10	2964842	Hexadecane	90	0.002	0.01
13.50	35308265	Caryophyllene oxide	95	0.029	0.17
14.13*	33918891	2,2′-Diethyl-1,1′-biphenyl	80	0.028	0.16
14.82	296612752	Tetradecanoic acid	99	0.243	1.44
15.12	42131403	(Z)-3-Hexadecene	98	0.035	0.20
15.47	295232200	Octadecane	98	0.242	1.43
16.18	4653356	2-Dodecen-1-yl (−) succinic anhydride	89	0.004	0.02
16.28	3384476	2-Methyl-1-hexadecanol	78	0.003	0.02
16.32	5094990	1-Pentadecene	92	0.004	0.02
17.33	34270249	2-Heptadecanol	78	0.028	0.17
17.52	34215482	2-(Tetradecyloxy)-ethanol	81	0.028	0.17
17.74	13953740	Hexadecane	90	0.011	0.07
17.87	18906884	Heneicosane	87	0.016	0.09
18.08	85618813	Pentadecanoic acid	97	0.070	0.41
18.19	151994108	1,2-Benzenedicarboxylic acid, bis (2)	86	0.125	0.74
18.50	2213315118	Cyclohaxadecane	99	1.816	10.71
18.65	45837144	Nonadecane	96	0.038	0.22
18.77	42293352	1-Nonadecene	90	0.035	0.20

Retention time (min)	Response (area)	Best match[1]	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
19.00	199692334	2-Hexadecanol	90	0.164	0.97
19.17	76550515	2-Heptadecanone	87	0.063	0.37
19.37	103194224	Caffeine	94	0.085	0.50
19.77	14872741	Docosane	86	0.012	0.07
20.02	102125171	1-Octadecene	97	0.084	0.49
20.20	96794873	1-Hexadecanol	86	0.079	0.47
20.39	57493519	3-Eicosene	97	0.047	0.28
20.91	2933718734	Dibutyl phthalate	83	2.407	14.20
21.24	114002736	Nonadecane	90	0.094	0.55
21.49	9672077	1-Nonadecene	86	0.008	0.05
21.76	122401077	1-Octadecene	99	0.100	0.59
22.43	51345191	3,5,6,7-Tetrah-s-indacen-1(2H)-one	81	0.042	0.25
22.54	4913720	Octadecane	95	0.004	0.02
22.63	33563860	1-Nonadecene	86	0.028	0.16
23.03	32829703	N-Methyl-N-[4-[4-methoxy-acetamide	90	0.027	0.16
23.15	82313597	2,3,5,6-Tetra-s-indacene-1,7-dione	76	0.068	0.40
23.48	857664501	5-Octadecene	97	0.704	4.15
24.01	15554319	Octadecane	90	0.013	0.08
24.35	140996042	16-Methyl-, met heptadecanoic acid	96	0.116	0.68
24.52*	95037913	5-Dodecyldihydro-2 (3H)-furanone	83	0.078	0.46
24.66	32387060	1-Henricosyl formate	90	0.027	0.16
25.01	14710926	(Z)-9-Tricosene	91	0.012	0.07
25.79	32371423	2-Hexyl-1-decanol	86	0.027	0.16
25.86	200623444	Hexadecanamide	93	0.165	0.97
26.00	32616620	1-Nonadecene	99	0.027	0.16
26.33	53218271	2-Dodecen-1-yl (−) succinic anhydride	86	0.044	0.26
26.65	7339051	2-Dodecen-1-yl (−) succinic anhydride	89	0.006022	0.04
27.09	56583135	Cis-11-Hexadecen-1-yl acetate	81	0.046430	0.27
27.21	129242826	1-Phenantthrenecarboxylic acid, 7-et	96	0.106053	0.63
27.36	10625426	1-Phenantthrenecarboxylic acid, 7-et	92	0.008719	0.05
27.51	17570838	Tricosane	98	0.014418	0.09
27.58	156887637	1-Nonadecene	98	0.128737	0.76
28.37	69739203	1,2,1-Phenanthrenecarboxylic acid	92	0.057226	0.34
28.73	20887801	Hexanedioic acid dioctyl ester	90	0.017140	0.10
28.95	98593890	1-Phenantthrenecarboxylic acid, 7-et	86	0.080903	0.48
29.10	627678209	1,2,1-Phenanthrenecarboxylic acid	99	0.515053	3.04
29.26	380114163	2-[(2-bu Cyclopropanenanoic acid	92	0.311910	1.84
30.65*	70574444	2H-1-Benzopyran-5-ol, 2-methyl-2-(4	94	0.057911	0.34

TABLE 4 (continued)

Retention time (min)	Response (area)	Best match[1]	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
30.75	85939990	Resocinol, 2-p-mentha-1,8-dien-3-y	98	0.0705	0.42
31.07	125006268	Tricosane	93	0.103	0.61
31.66	21935407	Acetamide, N-methyl-N-[4-[4-4methoxy	91	0.0180	0.11
31.83	432784246	Hexadecanoic acid, 2,3-dihyroxypro	74	0.355	2.10
32.46	10236345	Cyclotetradecane,1,7,11-trimethyl-	91	0.00840	0.05
32.58	2219980004	Dronabinol (THC)	99	1.82	10.75
32.72	63820716	Hexacosane	96	0.0524	0.31
33.23	27548366	1,3-Benzenediol,2-(3,7-dimethyl-2,	90	0.0226	0.13
33.43	33550885	Acetamide, N-methyl-N-[4-[4-4methoxy	94	0.0275	0.16
33.63	240628731	Cannabinol (CBN)	95	0.197	1.16
34.09	13044163	Cyclohexane, 1-(1,5-dimethylhexyl)-	86	0.0107	0.06
34.32	125757721	Heptacosane	99	0.103	0.61
34.52	197356583	1-Octdecanethiol	87	0.162	0.96
35.17	243624195	Octadecanoic acid, 2,3-dihydroxypro	86	0.200	1.18
35.86	69273621	Tricosane	92	0.0568	0.34
36.15	1676695684	Squalene	94	1.38	8.12
37.29	34686159	3-Eicosene, (E)-	91	0.0285	0.17
37.34	71189968	Heneicosane	96	0.0584	0.34
38.77	62069103	Heptacosane	95	0.0509	0.30
39.10	20150673	2-Dodecen-1-yl (−) succinic anhydride	94	0.0165	0.10
40.16	67270687	Heptacosane	97	0.0552	0.33
40.96	109391601	9-Hexadecenoic acid, eicosyl ester	76	0.0898	0.53
41.04	9230053	Cyclotetradecane, 1,7,11-trimethyl-	83	0.00757	0.04
41.50	30676052	Eicosane	91	0.0252	0.15
41.79	1169213328	Cholesterol[1]	99	0.959	5.66
42.27	45017056	9-Hexadecenoic acid, eicosyl ester	72	0.0369	0.22
42.61	16741293	Cholesteryl acetate	97	0.0137	0.08
42.69	4624026	Heneicosane, 3-methyl-	91	0.00379	0.02
42.80	36515665	Eicosane	90	0.0300	0.18
43.00	4896647	Heneicosane, 3-methyl-	91	0.00402	0.02
43.22	61362365	Cholesta-3,5-dien-7-one	96	0.0504	0.30
43.32	28641892	Cholesteryl acetate	99	0.0235	0.14
43.58	130345192	9-Hexadecenoic acid, eicosyl ester	91	0.107	0.63
43.86	206844252	Hexadecanoicacid, hexadecyl ester	95	0.170	1.00
44.15	31783685	Eicosane	83	0.0261	0.15
46.70	150517876	9-Hexadecenoic acid, eicosyl ester	83	0.124	0.73

Retention time (min)	Response (area)	Best match[1]	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
47.02	108047194	1-Octadecanethiol	84	0.0887	0.52
50.91	86165775	9-Hexadecenoic acid, eicosyl	83	0.0707	0.42

Total recovered (mg): 17.0**
Weight extracted (mg): 200
% recovered: 8.5**
** (Nominal semi-quantitative figures)

* Polynuclear aromatic hydrocarbons.

1 "Best match" compounds were determined by comparing the GC/MS output to the NBS standard reference library. They do not necessarily correspond to the true compound present in every case. For instance, the entry identified as "cholesterol" at retention time 41.79 is presumably something else, since cholesterol is not produced in plants. Most likely it is a wax-like fatty acid of similar molecular weight.

TABLE 5. GC/MS Semi-Quantitative Results: Solvated Extract Analysis; Combusted Sample

Retention time (min)	Response (area)	Best match	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
4.27	5371404	Phenol, 4-ethyl-	91	0.071	0.10
4.46	4820930	1H-Indene, 1-methyl-	91	0.063	0.09
4.62	11975267	1,2-Benzennediol	74	0.157	0.23
5.01	28398562	Naphthalene	91	0.373	0.53
5.17*	33292637	Benzofuran, 2,3-dihydro-	72	0.437	0.63
6.91	21443444	Indole	87	0.282	0.40
7.14	5635171	Naphthalene, 2-methyl-	95	0.074	0.11
7.45	5932574	Naphthalene, 2-methyl-	93	0.078	0.11
7.72	4757806	1,4-Benzenedoil, 2-methyl-	91	0.062	0.09
8.99	11013411	1H-Indole, 4-methyl-	90	0.145	0.21
9.32	60797737	Caryophyllene	99	0.798	1.15
9.71	4674849	1,6,10-Dodetatriene, 7,11-dimethyl-	96	0.061	0.09
9.97*	2209752	Naphthalene, 1,2,3,5,6,7,8,8a-octah	89	0.029	0.04
10.20	18874442	4,7,10-Cycloundecatriene	99	0.248	0.36
11.12	2060913	1H-3a,7-Methanoazulene,octahydro-1	90	0.027	0.04
11.20	2094526	Cylohexene, 1-methyl-4-(5-methyl-1	86	0.027	0.04
12.14*	13696523	Naphthalene, decahydro-4a-methyl-1-	92	0.180	0.26
12.33*	16059454	Naphthalene, 1,2,3,5,6,7,8,8a-octah	98	0.211	0.30
13.50	17021514	Caryophyllene oxide	96	0.223	0.32
13.59	4347127	1H-Cyclopropa [a]naphthalene,1a,2,3	98	0.057	0.08
14.75	2271757	10,10-Dimethylenebicyc	89	0.030	0.04

TABLE 5 (continued)

Retention time (min)	Response (area)	Best match	NBS Library match quality	Recovered conc. as pyrene (mg/g)	Recovered % of total
15.33	2173568	5-Azulenemethanol, 1,2,3,3a,4,5,6,7	86	0.029	0.04
15.67	26178775	.alpha.-Bisabolol	87	0.344	0.49
15.85	9580620	1-Decene	90	0.126	0.18
18.37	32298240	6-Octen-1-ol, 3,7-domethyl-, acetate	78	0.424	0.61
18.70	2422132	Diphenylethyne	90	0.032	0.05
21.24	4388527	Hexadecanoic acid	92	0.058	0.08
29.16	3509363	Glaucyl alcohol	86	0.046	0.07
30.63*	69664748	2H-1-Benzopyran-5-ol, 2-methyl-2-(4	95	0.915	1.31
30.73	75367485	Resorcinol, 2-pmemtha-1,8-dien-3-y	98	0.990	1.42
31.84	4625532	Delta.8-Tetrahydrocannabinol	91	0.061	0.09
32.59*[1]	4408666746	Dronabinol (THC)[1]	98	57.9	83.04
33.07*[1]	2029605	Dronabinol (THC)[1]	91	0.027	0.04
33.63	334263844	Cannabinol (CBN)	97	4.389	6.30
37.34	3583356	Docosane	96	0.047	0.07
41.22	25609584	Vitamine E	89	0.336	0.48
45.39	28142178	.beta.-Amyrin	95	0.369	0.53

Total recovered (mg): 69.7**
Weight extracted (mg): 200
% recovered: 35**
** (Nominal semi-quantitative figures)

* Polynuclear aromatic hydrocarbons.
[1] Significantly increased response resulting in peak splitting, thus two consecutive retention times.

the GC/MS did not provide an accurate measurement of cannabinoids.) Altogether, eight different PAHs were identified in the solvated extract and the gaseous headspace.

DISCUSSION

The major finding of this study was a drastic quantitative reduction in non-cannabinoid compounds in the vapor from the Volcano. This strongly suggests that vaporization is an effective method for delivering medically active cannabinoids while effectively suppressing other potentially deleterious compounds that are a byproduct of combustion.

Numerous outstanding questions about vaporization remain to be re-

searched. This study was not designed to measure the presence of toxic gases with low molecular weight, such as ammonia, hydrogen cyanide and carbon monoxide, which are known to be produced by marijuana cigarettes (Huber 1991; Institute of Medicine 1982). Previous studies have indicated a qualitative decrease in CO with vaporization, but this remains to be quantitatively measured. Neither did this study analyze the solid tar phase of the vapor for non-cannabinoids. However, there is sound reason to believe that the total amount of tar was drastically reduced, given the absence of detectable combustion. Unlike the combusted marijuana, which turned to ash, the vaporized sample remained greenish-brown and intact, though clearly dessicated.

Numerous unexplored variables could conceivably affect the efficiency and output of vaporization. Included are variations in temperature; differences in the density, weight, and consistency of material in the chamber; differences in the variety and potency of cannabis used; and use of different preparations such as hashish, hash oil, etc. Further research is needed to determine the extent of such effects.

The effects of vaporization are illustrated in Figure 3 from the manufacturer. The vaporized cannabis does not turn to ash, but retains its original shape, as discussed above. A microscopic examination reveals the physical nature of the process. The cannabinoids in cannabis are borne in droplets of resin, known as glandular trichomes, which coat the exterior structures of the flowering tops, and the leaves to a lesser extent. The trichomes resemble small stalks or protuberances, appearing like dewy-capped mushrooms under a microscope. After vaporization, the resin has evaporated and trichomes have withered, while the underlying vegetative matter remains intact. This confirms that vaporization is essentially a different physical process than combustion.

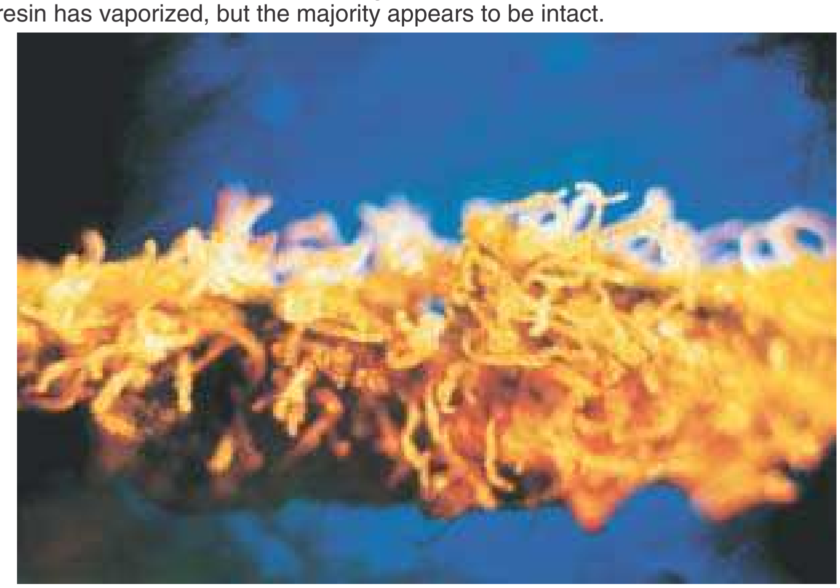
The efficacy of vaporization is further attested by the growing number of patients who have taken up vaporizers instead of smoking. Many users say they have ceased smoking marijuana altogether because they find it unduly irritating to their throat and lungs. Instead, they say, vaporization gives them the same therapeutic effects without any untoward irritation or sore throat. On the other hand, a few refractory individuals say they prefer the savor of smoke or claim not to feel the same impact from vapor. It should be noted that vaporizers do not entirely eliminate respiratory irritation. A puff of strong vaporized cannabis will occasionally elicit a cough. This could be entirely due to THC itself, which is known to irritate the bronchial tract (Tashkin 1977).

In summary, there is good reason to believe that vaporization is a highly effective method of smoke harm reduction. Nonetheless, at pres-

FIGURE 3. Cannabis before and after vaporization.

(A) Macrophoto of cannabis sample prior to vaporization showing trichomes with resin.

(B) Macrophoto after the first passage of hot air flow from the Volcano. Part of the resin has vaporized, but the majority appears to be intact.



(C) Macrophoto after several passages of hot air from the Volcano. The resin has disappeared, and trichomes have withered, but non-incinerated fibrous material remains.

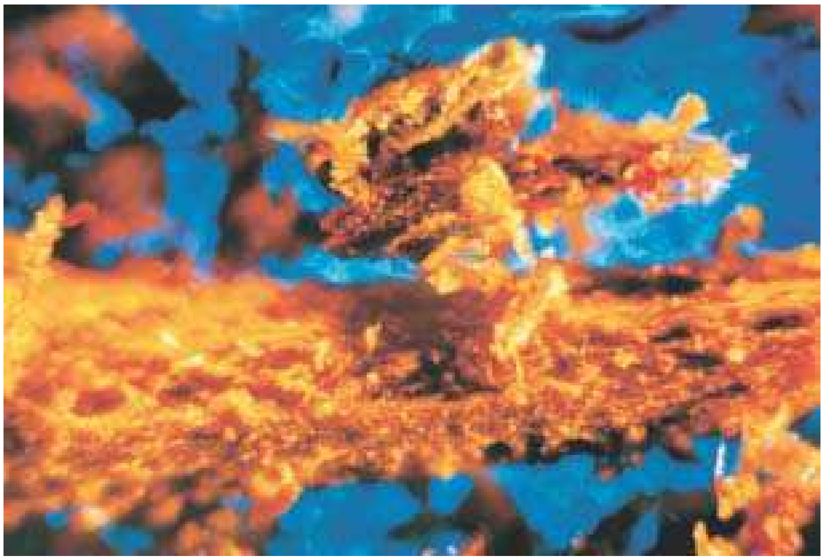


Figure 3 macrophotos reprinted with permission of Storz & Bickel <http://www.vapormed.de/en_anwndg.htm> 7/24/03.

ent smoked cigarettes from NIDA remain the only FDA approved method of administering cannabis to human subjects. The shortcomings of smoked marijuana have been widely viewed as an obstacle to approval of natural cannabis as a medicine. This view was expressed by the Institute of Medicine in its report on medical marijuana (IOM 1999, Executive Summary p. 8):

> Because of the health risks associated with smoking, smoked marijuana should generally not be recommended for long-term use . . .
>
> The goal of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but rather as a first step towards the possible development of non-smoked, rapid-onset delivery systems. However, it will likely be many years before a safe and effective cannabinoid delivery system, such as an inhaler, will be available for patients.

The IOM report failed to note that vaporizers appear to offer a feasible "non-smoked, rapid-onset delivery system."

A major goal of this study was to pave the way for vaporizers to be introduced into human studies, in particular studies of medical cannabis that are now normally conducted using NIDA cigarettes. Data from this study have been submitted to the FDA in support of an application for an investigational device exemption (IDE) to permit the Volcano to be used in a study by Dr. Donald Abrams of the University of California, San Francisco. The study, which is being supported by California's Center for Medicinal Cannabis Research, is essentially a Phase I study of vaporization. The protocol calls for testing inhaled cannabis of three different potencies in healthy test subjects. The study will compare subjective effects, cannabinoid blood levels and carbon monoxide levels in exhaled breath in subjects on six different days, three days smoking 400 mgs of NIDA marijuana of either 1.7% THC, 3.5% THC or 7% THC, and three days vaporizing identical amounts and strengths of NIDA marijuana.

The FDA currently has no criteria for evaluating vaporization devices. The only device now approved for administering marijuana to humans is NIDA pre-rolled cigarettes, which were approved before modern medical device regulations were enacted in 1976. At that time, there was no need for data on toxicity, dosage delivery, or the chemical content of the smoke delivered. Based on the evidence of this study, the Volcano should compare favorably in every respect. It remains to be seen whether the FDA will require additional pre-clinical tests before allowing the Volcano to be used in human subjects.

In any case, however, our research indicates that vaporization is a promising technology for smoke harm reduction. A growing number of vaporizers are now available through the internet (for a list, see http://www.canorml.org/healthfacts/vaporizers.html). They range from high-technology devices with medical grade components to simple hand-held glass pipes to be heated over a flame. Despite their obvious usefulness for medical cannabis patients, they have to be marketed as herbal vaporizers in order not to run afoul of federal drug paraphernalia laws. While usage of vaporizers is rapidly spreading, further testing and research are clearly needed to optimize vaporization technology.

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Clinical Pharmacodynamics of Cannabinoids

Franjo Grotenhermen

ABSTRACT. Our knowledge of the pharmacodynamics of cannabinoids, that is, "the study of the biochemical and physiologic effects of drugs and their mechanisms of action" (*The Merck Manual*), has considerably increased within the past decade due to the detection of an endogenous cannabinoid system with specific receptors and their endogenous ligands.

THC (Δ^9-tetrahydrocannabinol), the main source of the pharmacological effects caused by the use of cannabis including the medicinal benefits of the plant, is an agonist to both the CB_1 and the CB_2 subtype of these receptors. Its acid metabolite THC-COOH (11-nor-9-carboxy-THC), the non-psychotropic cannabidiol (CBD), analogues of these natural compounds, antagonists at the cannabinoid receptors and modulators of the endogenous cannabinoid system are also promising candidates for clinical research and therapeutic uses. Cannabinoid receptors are distributed in the central nervous system and many peripheral tissues (spleen, leukocytes; reproductive, urinary and gastrointestinal tracts; endocrine glands, arteries and heart, etc.). Additionally, there is evidence for non-receptor dependent mechanisms of cannabinoids.

Five endogenous cannabinoids, anandamide, 2-arachidonylglycerol, noladine ether, virodhamine, and NADA, have been detected. There is evidence that besides the two cannabinoid receptor subtypes cloned so far, additional cannabinoid receptor subtypes and vanilloid receptors are involved in the complex physiological functions of endocannabinoids that include, for example, motor coordination, memory procession, pain modulation and neuroprotection. Strategies to modulate their activity include inhibition of re-uptake into cells and inhibition of their degradation to increase concentration and duration of action.

Franjo Grotenhermen, MD, is affiliated with the nova-Institut, Goldenbergstraße 2, D-50354 Hürth, Germany (E-mail: franjo-grotenhermen@nova-institut.de).

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At doses exceeding the psychotropic threshold, ingestion of exogenous CB_1 receptor agonists or cannabis, respectively, usually causes an enhanced well-being and relaxation with an intensification of ordinary sensory experiences. The most important potential adverse acute effects caused by overdosing are anxiety and panic attacks, and with regard to somatic effects, increased heart rate and changes in blood pressure. Regular use of cannabis may lead to dependency and to a mild withdrawal syndrome. The existence and the intensity of possible long-term damages on psyche and cognition, immune system, fertility and on pregnancy remain controversial. They are reported to be low in humans and do not preclude a legitimate therapeutic use of cannabis based drugs.

Properties of cannabinoids that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects.

KEYWORDS. Cannabis, THC, cannabinoids, marijuana, pharmacodynamics, cannabinoid receptors, endocannabinoids, mechanism of action, therapeutic use, therapeutic potential, side effects, interaction

INTRODUCTION

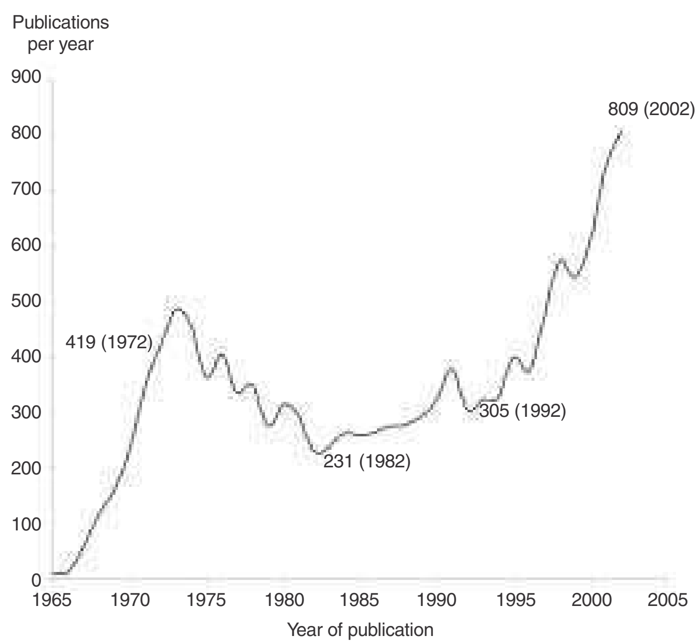
Unlike the opiates and many other medicinally used plant constituents, the cannabinoids were not identified before the 20th century, which occasionally resulted in dosing problems of oral medicinal extracts which had been in use in the 19th century in Europe and North America. In the 1930s and 1940s, the chemical structure of the first phytocannabinoids had been successfully characterized (Loewe 1950), and the first synthetic derivatives of THC (parahexyl, DMHP) were successfully tested in clinical studies for epilepsy (Davis and Ramsey 1949), depression (Stockings 1947) and dependency to alcohol and opiates (Thompson and Proctor 1953). However, it was not until 1964 that Δ^9-tetrahydrocannabinol (Δ^9-THC, dronabinol), mainly responsible for the pharmacological effects of the cannabis plant (Dewey 1986, Hollister 1986), was stereochemically defined, and synthesized (Gaoni and Mechoulam 1964). Another scientific breakthrough in cannabinoid

research was the detection of a system of specific cannabinoid receptors in mammals and their endogenous ligands within the past 15 years. Both detections resulted in a considerable boost in research activities (see Figure 1).

Cannabinoids were originally thought to be only present in the cannabis plant (*Cannabis sativa* L.), but recently some cannabinoid type bibenzyls have also been found in liverwort (*Radula perrottetii* and *Radula marginata*) (Toyota et al. 2002), the chemical structure of perrottetinenic acid in liverwort being similar to that of Δ^9-THC in cannabis.

About 65 cannabinoids have been detected in the cannabis plant, mainly belonging to one of 10 subclasses or types (ElSohly 2002), of which the cannabigerol type (CBG), the cannabichromene type (CBC), the cannabidiol type (CBD), the Δ^9-THC type (with nine cannabinoids), and the cannabinol type (CBN) are the most relevant in quantity. Cannabinoid distribution varies between different cannabis strains and

FIGURE 1. Dynamic of cannabinoid publications. Annual number of publications found in PubMed (http://www.ncbi.nlm.nih.gov/PubMed/) by using the keywords "cannabis, cannabinoids, THC, marijuana" between 1965 and 2002.



usually only three or four cannabinoids are found in one plant in relevant concentrations. Other cannabis compounds of possible pharmacological interest are terpenes (about 120) which are responsible for the specific smell of the plant, flavonoids (21), and nitrogenous compounds (27) including two spermidine type alkaloids.

Δ^9-THC, the main cannabinoid in cannabis of the drug type with concentrations in a range between 2 and 30% in the flowering tops and upper leaves of the female plant, given alone produced similar effects as whole plant drug cannabis (marijuana) in healthy volunteers (Hart et al. 2002, Wachtel et al. 2002) and patients (Abrams et al. 2001). In one study, pure THC and whole cannabis were either smoked or taken orally in a double-blind, crossover design with five experimental conditions: a low and a high dose of THC-only, a low and a high dose of whole-plant cannabis, and placebo (Wachtel et al. 2002). In both the oral study and the smoking study, THC-only and whole plant cannabis produced similar subjective effects, with only minor differences. The THC main effects, including medicinal properties, may be modulated by other cannabinoids, mainly CBD, and other cannabis constituents (McPartland and Russo 2001).

In addition to these phytocannabinoids, synthetic agonists and antagonists at the cannabinoid receptor and other modulators of the endogenous cannabinoid system are under investigation for therapeutic purposes.

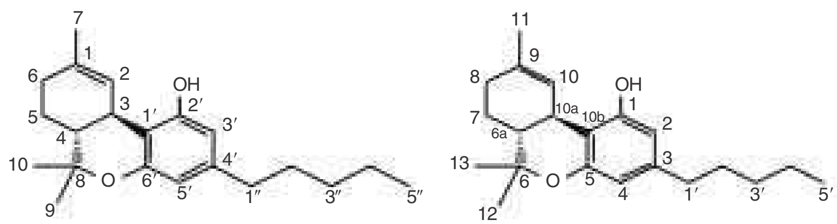
MECHANISM OF ACTION

The mechanism of action of cannabinoids is best investigated for Δ^9-THC (THC, dronabinol; see Figure 2 for chemical structure) and other cannabinoid receptor agonists, while the mode of action of other cannabinoids of therapeutic interest, among them CBD, as well as the carboxy metabolite of THC (11-nor-9-carboxy-Δ^9-THC) and its analogues (e.g., ajulemic acid, CT-3) is less well established. Previous reviws on cannabis include two by Grotenhermen (2002b,c).

Mechanism of Action of Δ^9-THC

The majority of THC effects are mediated through agonistic actions at cannabinoid receptors. Some non-CB mediated effects of THC and synthetic derivatives have also been described, e.g., some effects on the immune system (Bueb et al. 2001), some neuroprotective effects (Hampson

FIGURE 2. Chemical structure of THC, the main cannabinoid in the cannabis plant, according to the monoterpenoid system (Δ^1-THC) and dibenzopyran system (Δ^9-THC).



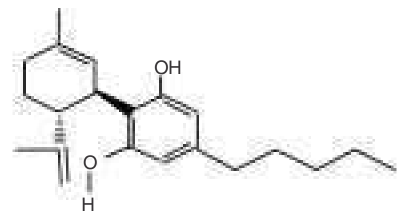
2002), and anti-emetic effects. The anti-emetic effects of THC are supposed to be mediated in part by CB_1 receptors (Parker et al. 2003) and in part by non-CB mechanisms, the rationale for the clinical use of THC as an anti-emetic in children receiving cancer chemotherapy (Abrahamov et al. 1995). Due to the lower CB_1 receptor density in the brain of children compared with adults, they tolerated relatively high doses of Δ^8-THC in a clinical study, without significant CB_1 receptor mediated adverse effects (Abrahamov et al. 1995). In a study with cells stably transfected with the human 5-HT_{3A} receptor, several (endo)cannabinoids (THC, WIN55,212-2, anandamide, etc.) directly inhibited currents induced by 5-hydroxytryptamine (Barann et al. 2002). Since 5-HT_3 antagonists are potent anti-emetic drugs, this may be one mechanism by which cannabinoids act as anti-emetics.

It is possible that several effects previously thought to be non-receptor mediated are mediated by cannabinoid receptor subtypes that have not yet been identified.

Mechanism of Action of Cannabidiol

The mode of action of cannabidiol (see Figure 3 for chemical structure) is not fully understood and several mechanisms have been proposed: (1) CBD acts as antagonist at the central CB_1 receptor and is able to inhibit several CB_1 mediated THC effects (Zuardi et al. 1982). In a study by Petitet et al. (1998), CBD considerably reduced the receptor activation by the potent classical CB_1 receptor agonist CP55940. (2) CBD stimulates the vanilloid receptor type 1 (VR_1) with a maximum effect similar in efficacy to that of capsaicin (Bisogno et al. 2001).

FIGURE 3. Cannabinoid.



(3) CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration (Bisogno et al. 2001, Mechoulam and Hanus 2002). (4) Finally, CBD may also increase the plasma THC level (Bornheim et al. 1995) by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system (Bornheim et al. 1998, Jaeger et al. 1996). However, there was no or minimal effect of CBD on plasma levels of THC in man (Agurell et al. 1981, Hunt et al. 1981).

In a study that analyzed the mode of action of the anti-inflammatory and anti-hyperalgesic effects of CBD, simultaneous administration of a VR_1 receptor antagonist fully reversed the anti-hyperalgesic effects (Costa et al. 2003). A CB_2 receptor antagonist was partly effective and a CB_1 receptor antagonist had no effect. The anti-inflammatory efficacy of CBD was unrelated to cyclooxygenase (COX) activity, but inhibited the endothelial isoform of nitric oxide synthase (eNOS). In a rat model of arthritis, low doses of CBD decreased prostaglandin E_2, nitric oxide and lipid peroxide level, mediators that are all known to be involved in the development and maintenance of arthritis (Costa et al. 2003).

CANNABINOID RECEPTORS

To date two cannabinoid receptors have been identified, the CB_1 (cloned in 1990), and the CB_2 receptor (cloned in 1993) (Pertwee 1997), exhibiting 48% amino acid sequence identity. Besides their difference in amino acid sequence, they differ in signaling mechanisms, tissue distribution, and sensitivity to certain agonists and antagonists that show marked selectivity for one or the other receptor type (Howlett et al. 2002). Both receptor types are coupled through inhibiting G proteins (G_i proteins), negatively to adenylate cyclase, and positively to mito-

gen-activated protein kinase. Activation of G_i proteins causes inhibition of adenylate cyclase, thus, inhibiting the conversion of ATP to cyclic AMP (cAMP). CB_1 receptors are also coupled to certain kinds of calcium channels and potassium channels (Pertwee 2002). They may also mobilize arachidonic acid and close 5-HT_3 receptor ion channels (Pertwee 2002). Under certain conditions, they may also activate adenylate cyclase through stimulating G proteins (G_s proteins) (Glass and Felder 1997).

CB_1 receptors are mainly found on neurons in the brain, spinal cord and peripheral nervous system, but are also present in certain peripheral organs and tissues, among them endocrine glands, leukocytes, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts (Pertwee 1997). In the central nervous system the CB_1 receptor is the most abundant G-protein coupled receptor. One of its functions is inhibition of neurotransmitter release. Their endogenous agonists probably serve as retrograde synaptic messengers. CB_1 receptors are highly expressed in the basal ganglia, cerebellum, hippocampus and dorsal primary afferent spinal cord regions, which reflect the importance of the cannabinoid system in motor control, memory processing and pain modulation, while their expression in the brainstem is low (Howlett et al. 2002), which may account for the lack of cannabis-related acute fatalities, e.g., due to depression of respiration.

CB_2 receptors occur principally in immune cells, among them leukocytes, spleen and tonsils (Pertwee 2002). In contrast to CB_1 receptors they are not coupled to ion channels. Immune cells also express both CB_1 receptors but there is markedly more mRNA for CB_2 than CB_1 receptors in the immune system. Levels of CB_1 and CB_2 mRNA in human leukocytes have been shown to vary with cell type (B cells > natural killer cells > monocytes > polymorphonuclear neutrophils, T4 and T8 cells) (Galiègue et al. 1995). One of the functions of CB receptors in the immune system is modulation of cytokine release.

Activation of the CB_1 receptor produces marijuana-like effects on psyche and circulation, while activation of the CB_2 receptor does not. Hence, selective CB_2 receptor agonists have become an increasingly investigated target for therapeutic uses of cannabinoids, among them analgesic, anti-inflammatory and anti-neoplastic actions (Recht et al. 2001, Sanchez et al. 2001).

There is increasing evidence for the existence of additional cannabinoid receptor subtypes in the brain and periphery (Breivogel et al. 2001, Di Marzo et al. 2000, Fride et al. 2003, Wiley and Martin 2002). These receptors are more likely to be functionally related to the known

cannabinoid receptors than have a similar structure as there is no evidence for additional cannabinoid receptors in the human genome (Baker et al. 2003).

ENDOCANNABINOIDS

The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, endogenous cannabinoids or endocannabinoids, a family of eicosanoids (Devane et al. 1992, Giuffrida et al. 2001, Sugiura et al. 1995). To date five endocannabinoids have been identified. These are *N*-arachidonylethanolamide (anandamide) (Devane et al. 1992), 2-arachidonylglycerol (2-AG) (Mechoulam et al. 1995, Sugiura et al. 1995), 2-arachidonylglyceryl ether (noladin ether) (Hanus et al. 2001), *O*-arachidonyl-ethanolamine (virodhamine) (Porter et al. 2002), and *N*-arachidonyl-dopamine (NADA) (Huang et al. 2002).

Cannabinoid receptors and their endogenous ligands together constitute the "endogenous cannabinoid system," or the "endocannabinoid system" which is teleologically millions of years old and has been found in mammals and many other species (De Petrocellis et al. 1999).

Endocannabinoids serve as neurotransmitters or neuromodulators (Howlett 2002). Anandamide and NADA do not only bind to cannabinoid receptors but also stimulate vanilloid receptors (VR_1) (Al-Hayani et al. 2001, Huang et al. 2002), non-selective ion channels associated with hyperalgesia. Thus, the historical designation of anandamide as an "endocannabinoid" seems to be only one part of the physiological reality, and cannabinoid receptors seem to amount only to some of the "anandamide receptors." Some non CB effects may be mediated by vanilloid receptors, e.g., inhibition of cell proliferation of rat C6 glioma cells by endocannabinoids was reported to involve combined activation of both vanilloid receptors and to a lesser extent cannabinoid receptors (Jacobsson et al. 2001).

The first two discovered endocannabinoids, anandamide (Figure 4) and 2-AG (Figure 5), are the best to be studied. They are produced "on demand" by cleavage of membrane lipid precursors and released from cells in a stimulus-dependent manner (Giuffrida et al. 2001). The production of anandamide and 2-AG involves phospholipases D and C. After release, they are rapidly deactivated by uptake into cells and metabolized. Metabolism of anandamide and 2-AG occurs by enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) (Di Marzo 1998, Giuffrida

FIGURE 4. Arachidonylethanolamide (anandamide).

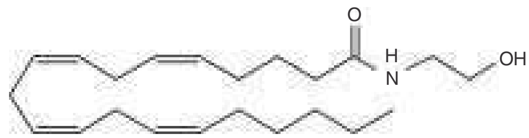
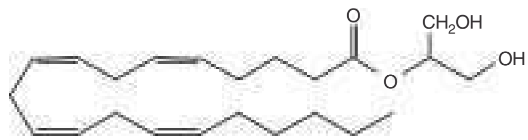


FIGURE 5. 2-Arachidonylglycerol (2-AG).



et al. 2001). FAAH degrades anandamide to arachidonic acid and ethanolamide. In mice, lack of FAAH resulted in supersensitivity to anandamide and enhanced endogenous cannabinoid signalling (Cravatt et al. 2001). Other metabolic processes include hydrolysis of 2-AG by monoglyceride lipase (Dinh et al. 2002), acylation of noladin ether (Fezza et al. 2002), oxidation of anandamide and 2-AG and methylation of the aromatic moiety of NADA.

In all cases cellular uptake must preceed metabolism since metabolism occurs only in the cells. Endocannabinoid uptake by cells seems to happen by "enhanced diffusion" through the cell membrane (Fowler and Jacobsson 2002, Huang et al. 2002, Porter et al. 2002), even though an active carrier system has not been detected so far. Simple passive diffusion following a concentration gradient into the cells, where they are quickly metabolized by FAAH, is regarded as unlikely, since several substances have been developed that are thought to inhibit anandamide cellular uptake without inhibiting FAAH, among them Arvanil (Di Marzo et al. 2002) and VDM11 (Baker et al. 2001), and noladine ether and NADA are rapidly taken up into cells despite they are rather stable or refractory to enzymatic hydrolysis (Fezza et al. 2002, Huang et al. 2002). However, the discussion on the existence of a transport system is not finished, and one group demonstrated that arvanil and other substances regarded as anandamide transporters (olvanil, AM404) were actually inhibitors of FAAH (Glaser et al. 2003). Intracellular uptake of endocannabinoids is a temperature dependent and rapid process with a

half time of a few minutes, compared to hours in the case of exogenous plant cannabinoids.

AFFINITY TO THE CANNABINOID RECEPTOR

Cannabinoids show differing affinities for CB_1 and CB_2 receptors. Synthetic cannabinoids have been developed that act as highly selective agonists or antagonists at one of these receptor types (Abadji et al. 1994, Pertwee 1999b, Pertwee 2002). Δ^9-THC has approximately equal affinity for the CB_1 and CB_2 receptor, while anandamide has marginal selectivity for CB_1 receptors (Pertwee 1999b). However, the efficacy of THC and anandamide is less at CB_2 than at CB_1 receptors. In contrast to the anandamide, 2-AG and noladine ether which act as agonists at both CB receptor types, virodhamine acts as an antagonist at the CB_1 receptor and as a full agonist at the CB_2 receptor (Porter et al. 2002).

TONIC ACTIVITY OF THE ENDOCANNABINOID SYSTEM

When administered by themselves, cannabinoid receptor antagonists may behave as inverse agonists in several bioassay systems, i.e., not only block the effects of exogenous cannabinoids but produce effects that are opposite in direction from those produced by cannabinoid receptor agonists, e.g., cause hyperalgesia (Jaggar 1998), suggesting that the endogenous cannabinoid system is tonically active. Tonic activity may be due to a constant release of endocannabinoids or from a portion of cannabinoid receptors that exist in a constitutively active state (Pertwee 2002).

Tonic activity of the endogenous cannabinoid system has been demonstrated in several conditions. Endocannabinoids have been shown to be tonically active in the dorsal horn neurons of the spinal cord, thus, attenuating acute nociceptive transmission at the level of the spinal cord (Chapman 1999). Endocannabinoid levels have been demonstrated to be increased in a pain circuit of the brain (periaqueductal gray) following painful stimuli (Walker et al. 1999). Tonic control of spasticity by the endocannabinoid system has been observed in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice, an animal model of multiple sclerosis (Baker et al. 2001). An increase of cannabinoid receptors following nerve damage was demonstrated in a

rat model of chronic neuropathic pain (Siegling et al. 2001) and in a mouse model of intestinal inflammation (Izzo et al. 2001). This may increase the potency of cannabinoid agonists used for the treatment of these conditions. Tonic activity has also been demonstrated with regard to appetite control (Di Marzo et al. 2000b) and with regard to vomiting in emetic circuits of the brain (Darmani 2001). Elevated endocannabinoid levels have been detected in cerebrospinal fluid of schizophrenic patients (Leweke et al. 1999). In other models tonic or enhanced activity could not be demonstrated, e.g., in a rat model of inflammatory hyperalgesia (Beaulieu et al. 2000).

PHARMACOLOGICAL EFFECTS OF THC

The pharmacological activity of Δ^9-THC is stereoselective, with the natural (−)-trans isomer (dronabinol) being 6-100 times more potent than the (+)-trans isomer, depending on the assay (Dewey 1986).

The activation of the cannabinoid system through THC and other phytocannabinoids, synthetic and endogenous cannabinoids causes numerous actions that have been extensively reviewed (see Table 1) (Adams and Martin 1996, Dewey 1986, Grotenhermen and Russo 2002, Hall et al. 1994, Hollister 1986, House of Lords 1998, Joy et al. 1999, Kalant et al. 1999). Additional non-receptor mediated effects have come into focus as well (Hampson 2002). Some effects of cannabinoid receptor agonists show a biphasic behavior in dependency of dose, e.g., low doses of anandamide stimulated phagocytosis and stimulated behavioral activities in mice while high doses decreased activities and caused inhibitory effects on immune functions (Sulcova et al. 1998).

TOXICITY

The median lethal dose (LD_{50}) of oral THC in rats was 800-1900 mg/kg depending on sex and strain (Thompson et al. 1973). There were no cases of death due to toxicity following the maximum oral THC dose in dogs (up to 3000 mg/kg THC) and monkeys (up to 9000 mg/kg THC) (Thompson et al. 1973). Acute fatal cases in humans have not been substantiated. However, myocardial infarction may be triggered by THC due to effects on circulation (Bachs and Morland 2001, Mittleman et al. 2001). However, this is unlikely to occur in healthy subjects, but possibly

TABLE 1. Effects of THC. The Following Dose-Dependent Effects Were Observed in Clinical Studies, *in vivo*, or *in vitro*

Psyche and perception. Fatigue, euphoria, enhanced well-being, dysphoria, anxiety, reduction of anxiety, depersonalization, increased sensory perception, heightened sexual experience, hallucinations, alteration of time perception, aggravation of psychotic states, sleep.
Cognition and psychomotor performance. Fragmented thinking, enhanced creativity, disturbed memory, unsteady gait, ataxia, slurred speech, weakness, deterioration or amelioration of motor coordination.
Nervous system. Analgesia, muscle relaxation, appetite stimulation, vomiting, anti-emetic effects, neuroprotection in ischemia and hypoxia.
Body temperature. Decrease of body temperature.
Cardiovascular system. Tachycardia, enhanced heart activity, increased output, increase in oxygen demand, vasodilation, orthostatic hypotension, hypertension (in horizontal position), inhibition of platelet aggregation.
Eye. Injected (reddened) conjunctivae, reduced tear flow, decrease of intraocular pressure.
Respiratory system. Bronchodilation, hyposalivation and dry mouth.
Gastrointestinal tract. Reduced bowel movements and delayed gastric emptying.
Hormonal system. Influence on LH, FSH, testosterone, prolactin, somatotropin, TSH, glucose metabolism, reduced sperm count and sperm motility, disturbed menstrual cycle and suppressed ovulation.
Immune system. Impairment of cell-mediated and humoral immunity, immune stimulation, anti-inflammatory and anti-allergic effects.
Fetal development. Malformations, growth retardation, impairment to fetal and postnatal cerebral development, impairment of cognitive functions.
Genetic material and cancer: Antineoplastic activity, inhibition of synthesis of DNA, RNA and proteins.

in persons with coronary heart disease for whom orthostatic hypotension or a moderately increased heart rate may pose a risk.

Adverse effects of medical cannabis use are within the range of effects tolerated for other medications (House of Lords 1998, Joy et al. 1999). It is controversial whether heavy regular consumption may impair cognition (Pope et al. 2001, Pope 2002, Solowij et al. 2002), but this impairment seems to be minimal if it exists (Lyketsos et al. 1999, Pope et al. 2001). Early users who started their use before the age of 17 presented with poorer cognitive performance, especially verbal IQ compared to users who started later or non-users (Pope et al. 2003). Possible reasons for this difference may be (1) innate differences between groups in cognitive ability, antedating first cannabis use; (2) a neurotoxic

effect of cannabis on the developing brain; or (3) poorer learning of conventional cognitive skills by young cannabis users who have eschewed school and university (Pope et al. 2003).

Long-term medical use of cannabis for more than 15 years has been reported to be well-tolerated without significant physical or cognitive impairment (Russo et al. 2002). There is conflicting evidence that infants exposed to THC *in utero* suffer developmental and cognitive impairment (Fried et al. 1998). Marihuana can induce a schizophrenic psychosis in vulnerable persons (Hall et al. 1994, Solowij and Grenyer 2002b) and there is increasing evidence that there is a distinct cannabis psychosis (Nunez and Gurpegui 2002).

The harmful effects of combustion products produced by smoking cannabis have to be distinguished from effects by cannabis or single cannabinoids (Joy et al. 1999).

PSYCHE, COGNITION AND BEHAVIOR

In many species the behavioral actions of low doses of THC are characterized by an unique mixture of depressant and stimulant effects in the CNS (Dewey 1986).

In humans, THC or cannabis consumption is usually described as a pleasant and relaxing experience. Use in a social context may result in laughter and talkativeness. Occasionally there are unpleasant feelings such as anxiety that may escalate to panic. A sense of enhanced well-being may alternate with dysphoric phases. THC improves taste responsiveness and enhances the sensory appeal of foods (Mattes et al. 1994). It may induce sleep (Freemon 1972, Lissoni et al. 1986).

Acute THC intoxication impairs learning and memory (Hampson and Deadwyler 1999, Heyser et al. 1993, Slikker et al. 1992), and may adversely affect psychomotor and cognitive performance (Solowij and Grenyer 2002b), reducing the ability to drive a car and to operate machinery. Reduced reaction time also affects the response of the pupil of the eye. A brief light flash shows decreased amplitude of constriction and a decelerated velocity of constriction and dilation (Kelly et al. 1993).

The most conspicuous psychological effects of THC in humans have been divided into four groups: affective (euphoria and easy laughter), sensory (increased perception of external stimuli and of the person's own body), somatic (feeling of the body floating or sinking in the bed), and cognitive (distortion of time perception, memory lapses, difficulty in concentration) (Perez-Reyes 1999).

These effects only appear if an individually variable threshold of dose is exceeded. During a study on the efficacy of dronabinol (THC) in 24 patients with Tourette syndrome who received up to 10 mg THC daily for 6 weeks, no detrimental effects were seen on neuropsychological performance (learning, recall of word lists, visual memory, divided attention) (Müller-Vahl et al. 2003a).

CENTRAL NERVOUS SYSTEM AND NEUROCHEMISTRY

Most THC effects (analgesia, appetite enhancement, muscle relaxation, hormonal actions, etc.) are mediated by central cannabinoid receptors, their distribution reflecting many of the medicinal benefits and side effects (Hampson and Deadwyler 1999, Pertwee 2002, Sañudo-Peña et al. 1999).

Cannabinoids interact with a multitude of neurotransmitters and neuromodulators (Dewey 1986, Pertwee 1992), among them acetylcholine, dopamine, α-aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptides (see Table 2). A number of pharmacological effects can be explained (at least in part) on the basis of such interactions. For example, tachycardia and hyposalivation with dry mouth (Domino 1999, Mattes et al. 1994) are mediated by effects of THC on release and turn-over of acetylcholine (Domino 1999). In a rat model, cannabinoid agonists inhibited activation of 5-HT_3 receptors, explaining antiemetic properties of cannabinoids to be based on interactions with serotonin (Fan 1995). Therapeutic effects in movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutamergic and dopaminergic transmitters systems (Müller-Vahl et al. 2002b, Musty and Consroe 2002).

Cannabinoids influence the activity of most neurotransmitters in a complex manner, which sometimes may result in contradictory effects with suppression or induction/intensification of convulsion, emesis, pain and tremor depending on subject and condition. Cannabis and dronabinol are used against nausea and vomiting caused by anti-neoplastic drugs but rarely may cause vomiting. They are used as analgesics but sometimes may increase pain, etc. These observations are probably based on the control of these effects by several neuronal circuits influenced by cannabinoids. Influence on neurotransmitters may depend on brain region. Thus, dopamine activity may be reduced by cannabinoids in brain areas responsible for motor control (Giuffrida et

TABLE 2. Neurotransmitter Functions Under Cannabinoid Control (Modified According to Baker et al. 2003)

Neurotransmitter	Associated disorder
Excitatory amino acids	
Glutamate	Epilepsy, nerve-cell death in ischemia and hypoxia (stroke, head trauma, nerve gas toxicity)
Inhibitory amino acids	
GABA	Spinal cord motor disorders, epilepsy, anxiety
Glycine	Startle syndromes
Monoamines	
Noradrenaline	Autonomic homeostasis, hormones, depression
Serotonin	Depression, anxiety, migraine, vomiting
Dopamine	Parkinson's disease, schizophrenia, vomiting, pituitary hormones, drug addiction
Acetylcholine	Neuromuscular disorders, autonomic homeostasis (heart rate, blood pressure), dementia, parkinsonism, epilepsy, sleep-wake cycle
Neuropeptides	Pain, movement, neural development, anxiety

al. 1999) but enhanced in the reward system (Gardner 2002). Interactions of cannabinoids with other neurotransmitter systems may cause unexpected effects. While studies in animals have demonstrated that opioid receptor antagonists precipitated a cannabinoid-like withdrawal syndrome in cannabinoid-dependent rats (Lichtman et al. 2001) and blocked other effects related to behavioral effects of CB_1 agonists (Braida et al. 2001, Tanda et al. 1997), in humans opioid receptor antagonists did not block the subjective effects of THC in one study (Wachtel and de Wit 2000) or even increased the subjective effects THC in another study (Haney et al. 2003).

One important physiological role of endocannabinoids seems to be neuroprotection (Mechoulam 2002). Ischemia and hypoxia in the CNS induce abnormal glutamate hyperactivity and other processes that cause neuronal damage. These processes also play a role in chronic neurodegenerative diseases such as Parkinson's and Alzheimer's disease and

multiple sclerosis. Neuroprotective mediators are also released in ischemia and hypoxia, including anandamide and 2-AG. When these two cannabinoids were administered after traumatic brain injury in animals, they reduced brain damage (Mechoulam 2002). Neuroprotective cannabinoid mechanisms observed in animal studies include reduction of glutamate toxicity by inhibition of excessive glutamate production, inhibition of calcium influx into cells, anti-oxidant properties which reduce damage caused by oxygen radicals and modulation of vascular tone (Grundy 2002, Hampson 2002, Mechoulam 2002). THC was neuroprotective in rats given the toxic agent ouabain. THC treated animals showed reduced volume of edema by 22% in the acute phase and 36% less nerve damage after 7 days (van der Stelt et al. 2001). Whether these effects may be of therapeutic benefit in acute or chronic diseases has to be elucidated. Clinical studies under way investigating the therapeutic potential of a non-psychotropic derivative of THC in acute conditions (head trauma, stroke and nerve gas intoxication) showed initial positive results (Knoller et al. 2002).

CIRCULATORY SYSTEM

THC can induce tachycardia (Perez-Reyes 1999) and increase cardiac output with increased cardiac labor and oxygen demand (Tashkin et al. 1977). It can also produce peripheral vasodilation, orthostatic hypotension (Benowitz and Jones 1975, Hollister 1986) and reduced platelet aggregation (Formukong et al. 1989). There was no change of mean global cerebral blood flow after smoking cannabis but increases and decreases in several regions (O'Leary et al. 2002).

In young healthy subjects the heart is under control of the vagus which mediates bradycardia. Tachycardia by THC may easily be explained by vagal inhibition (inhibited release of acetylcholine) through presynaptic CB_1 receptors (Szabo et al. 2001), which can be attenuated by beta-blockers (Perez-Reyes 1999) and blocked by the selective CB_1 antagonist SR141716A (Huestis et al. 2001). Regular use can lead to bradycardia (Benowitz and Jones 1975). The endogenous cannabinoid system seems to play a major role in the control of blood pressure. Hypotension is mediated by central inhibition of the sympathetic nervous system, obviously by activation of CB_1 receptors since this effect can also be prevented by a CB_1 antagonist (Lake et al. 1997). Endocannabinoids are produced by the vascular endothelium, circulating macrophages and platelets (Wagner et al. 1998). Vascular resistance in

the coronaries and the brain is lowered primarily by direct activation of vascular cannabinoid CB_1 receptors (Wagner et al. 2001).

SOME OTHER ORGAN SYSTEMS AND EFFECTS

Antibacterial and antiviral actions. Antibacterial actions have been demonstrated for CBD, CBG and THC (Van Klingeren and Ten Ham 1976). Incubation with THC reduced the infectious potency of herpes simplex viruses (Lancz et al. 1991).

Appetite and eating. The endogenous cannabinoid system plays a critical role in milk ingestion of newborn mice (Fride et al. 2003). Blockade of the CB_1 receptor results in death of newborns in this setting (Fride and Shohami 2002). Anandamide induces overeating in rats through a CB_1 receptor mediated mechanism (Williams and Kirkham 1999). Endocannabinoids in the hypothalamus are part of the brain's complex system for controlling appetite which is regulated by leptin (Di Marzo et al. 2001). Leptin is the primary signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. Leptin reduces food intake by upregulating appetite-reducing neuropeptides, such as alpha-melanocyte-stimulating hormone, and downregulating appetite-stimulating factors, primarily neuropeptide Y. In animal research reduced levels of leptin were associated with elevated levels of endocannabinoids in the hypothalamus, and application of leptin reduced endocannabinoid levels (Di Marzo et al. 2001). Cannabinoid induced eating is ascribed to an increase of the incentive value of food (Williams and Kirkham 2002).

Bones. Preliminary observations show that endocannabinoids seem to stimulate bone formation (Mechoulam et al. 2003). Reverse transcription polymerase chain reaction of differentiating osteoblastic precursor cells demonstrated progressive increase in mRNA levels of CB_2 but not of CB_1. In addition, normal mice treated systematically with 2-AG showed a dose dependent increase in trabecular bone formation (Mechoulam et al. 2003). The peptide leptin is known to negatively regulate both osteoblastic and endocannabinoid activity (Di Marzo et al 2001).

Digestive tract. Cannabinoid agonists inhibit gastrointestinal motility and gastric emptying in rats (Shook and Burks 1989). In a study with humans, THC caused a significant delay in gastric emptying (McCallum et al. 1999). In addition, CB agonists inhibited pentagastrin-induced gastric acid secretion in the rat (Coruzzi et al. 1999), mediated by sup-

pression of vagal drive to the stomach through activation of CB_1 receptors (Adami et al. 2002).

Eye. The evidence of cannabinoid receptors at different sites (anterior eye, retina, corneal epithelium) suggests that cannabinoids influence different physiological functions in the human eye (Pate 2002). Vasodilation in the eye is observed as conjunctival reddening after THC exposure (Dewey 1986). THC and some other cannabinoids decrease intraocular pressure (Colasanti 1990, Pate 2002). CB_1 receptors in the eye are involved in this effect while CB_2 receptor agonists do not reduce intraocular pressure (Laine et al. 2003).

Genetic and cell metabolism. THC can inhibit DNA, RNA, and protein synthesis, and can influence the cell cycle. However, very high doses are required to produce this effect *in vitro* (Tahir et al. 1992). Cannabinoid agonists inhibited human breast cancer cell proliferation *in vitro* (De Petrocellis et al. 1998, Melck et al. 2000), and, directly applied at the tumor site, showed antineoplastic activity against malignant gliomas in rats (Galve-Roperh et al. 2000).

Hormonal system and fertility. THC interacts with the hypothalamic-pituitary adrenal axis influencing numerous hormonal processes (Murphy 2002). Minor changes in human hormone levels due to acute cannabis or THC ingestion usually remain in the normal range (Hollister 1986). Tolerance develops to these effects, however, and even regular cannabis users demonstrate normal hormone levels.

Immune system. Animal and cell experiments have demonstrated that THC exerts complex effects on cellular and humoral immunity (Cabral 2002, Melamede 2002). It is not clear whether and to what extent these effects are of clinical relevance in humans with respect to beneficial inflammation (Evans et al. 1987, Sofia et al. 1973), allergies (Jan et al. 2003), autoimmune processes (Melamede 2002) and undesirable effects (decreased resistance towards pathogens and carcinogens) (Cabral 2002). THC was shown to modulate the immune response of T lymphocytes (Yuan et al. 2002). It suppressed the proliferation of T cells and changed the balance of T helper 1 (Th1) and T helper 2 (Th2) cytokines. It decreased the pro-inflammatory Th1 reaction (e.g., the production of interferon-gamma) and increased the Th2 reaction. This may explain why THC is effective against inflammation with a strong Th1 reaction, e.g., in multiple sclerosis, Crohn's disease and arthritis. The regulation of the activation and balance of human Th1/Th2 cells seems to be mediated by a CB_2 receptor-dependent pathway (Yuan et al. 2003).

Sperm. After several weeks of daily smoking 8-10 cannabis cigarettes, a slight decrease in sperm count was observed in humans, with-

out impairment of their function (Hembree et al. 1978). In animal studies high doses of cannabinoids inhibited the acrosome reaction (Chang et al. 1993).

PHARMACOLOGICAL ACTIVITY OF THC METABOLITES

11-Hydroxy-Δ9-THC

The most important psychotropic metabolite of Δ^9-THC is 11-OH-Δ^9-tetrahydrocannabinol (11-OH-THC) (Figure 6), with a similar spectrum of actions and similar kinetic profiles as the parent molecule (Lemberger et al. 1972, Perez-Reyes et al. 1972). After intravenous administration in humans, 11-OH-THC was equipotent to THC in causing psychic effects and reduction in intraocular pressure (Perez-Reyes et al. 1972). In some pharmacological animal tests, 11-OH-THC was 3 to 7 times more potent than THC (Karler and Turkanis 1987).

11-Nor-9-Carboxy-Δ9-THC

The most important non-psychotropic metabolite of Δ^9-THC is 11-nor-9-carboxy-THC (THC-COOH) (Figure 7). It possesses anti-inflammatory and analgesic properties by mechanisms similar to non-steroidal anti-inflammatory drugs (Burstein et al. 1989, Burstein 1999, Doyle et al. 1990). THC-COOH antagonizes some effects of the parent drug through an unknown mechanism, e.g., the cataleptic effect in mice (Burstein et al. 1987). Ajulemic acid (CT-3), a synthetic derivative of THC-COOH, shows a similar pharmacological profile as the natural substance. Recently, a possible mechanism of action was proposed for this derivative (Liu et al. 2003). Ajulemic acid bounds directly and specifically to the peroxisome proliferator-activated receptor gamma (PPAR gamma), a pharmacologically important member of the nuclear receptor

FIGURE 6. 11-OH-THC (11-hydroxy-Δ^9-THC).

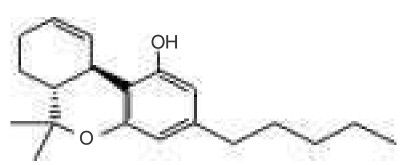
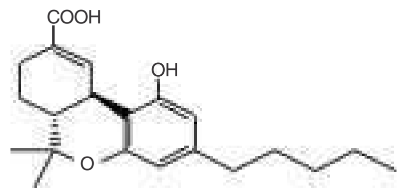


FIGURE 7. THC-COOH (11-nor-9-carboxy-Δ^9-THC).



superfamily. In addition, it was shown that ajulemic acid inhibited interleukin-8 promoter activity in a PPAR gamma-dependent manner, suggesting a link between the anti-inflammatory action of the cannabinoid acid and the activation of PPAR gamma.

PHARMACOLOGICAL EFFECTS OF OTHER CANNABINOIDS

Phytocannabinoids

Cannabidiol (CBD) is a non-psychotropic cannabinoid, for which sedating (Zuardi et al. 2002), anti-epileptic (Karler and Turkanis 1981), anti-dystonic (Consroe et al. 1986), anti-emetic (Parker et al. 2002), and anti-inflammatory (Malfait et al. 2000) effects have been observed. It reduced intraocular pressure (Colasanti et al. 1984), was neuroprotective (Hampson 2002), and antagonized the psychotropic and several other effects of THC (Zuardi et al. 1982). Anxiolytic and anti-psychotic properties might prove useful in psychiatry (Zuardi et al. 1982, Zuardi et al. 2002).

The non-psychotropic cannabinoids cannabigerol (CBG) and cannabichromene (CBC) showed sedative effects. CBG has been observed to decrease intraocular pressure (Colasanti 1990), showed antitumor activity against human cancer cells (Baek et al. 1998) and has antibiotic properties.

Endocannabinoids

Anandamide (arachidonylethanolamide), an endocannabinoid, produces pharmacological effects similar to those of THC. However, there are apparently some significant differences to THC. Under certain circumstances, anandamide acts as a partial agonist at the CB_1 receptor (Fride et al. 1995), and very low doses of anandamide antagonized the actions of THC. It is assumed that low doses of anandamide activated stimulating G_s protein pathways and not inhibiting G_i proteins, or

caused an allosteric modulation of the cannabinoid receptor (Fride et al. 1995).

Classical Synthetic Cannabinoids

Among the classical synthetic cannabinoids that retain the phytocannabinoid ring structures and their oxygen atoms are nabilone (Figure 8), HU-210, and HU-211 (Figure 9). Nabilone is available on prescription in several countries with a similar pharmacological profile as THC (Archer et al. 1986). HU-210, an analogue of Δ^8-THC with a dimethylheptyl side chain, is between 80 and 800 times more active than THC (Little et al. 1989, Ottani and Giuliani 2001), while its enantiomer (mirror image) HU-211 is completely devoid of psychoactivity (Titishov et al. 1989). The latter, also called dexanabinol, is an NMDA antagonist with neuroprotective properties in hypoxia and ischemia (Mechoulam and Shohami 2002). It is under clinical investigation for the treatment of brain injuries and stroke (Mechoulam and Shohami 2002). CT-3 or ajulemic acid (Figure 10), a derivative of the Δ^8-THC metabolite THC-COOH, is under clinical investigation for the treatment of inflammation and pain (Burstein 2002, Perez-Reyes et al. 1976).

FIGURE 8. Nabilone.

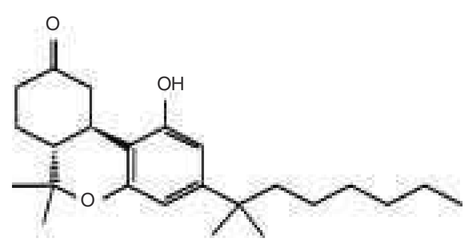


FIGURE 9. Dexanabinol (HU211).

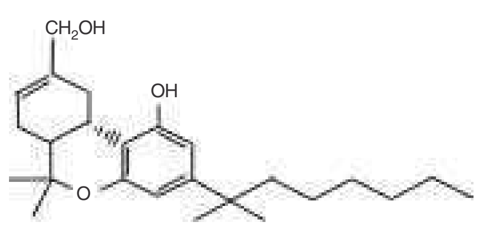
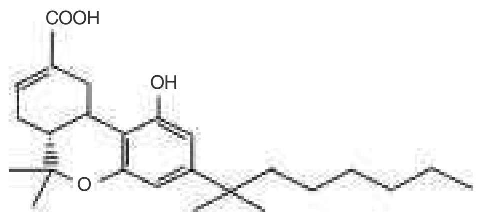


FIGURE 10. CT-3 (ajulemic acid).



Non-Classical Synthetic Cannabinoids

Levonantradol, from Pfizer, under clinical investigation for the treatment of pain (Jain et al. 1981) and the side effects of chemotherapy (Citron et al. 1985) and radiotherapy (Lucraft and Palmer 1982), is a non-classical cannabinoid with a more radical deviation of the typical structure. Other non-classical cannabinoids are the aminoalkylindol WIN-55,212-2, which has a 6.75-fold selective affinity towards the CB_2 receptor (Showalter et al. 1996) and the bicyclic cannabinoid analogue CP-55,940, a widely-used agonist for the testing of cannabinoid receptor affinity, with potency 4-25 times greater than THC, depending on assay (Melvin et al. 1993).

Anandamide Analogues

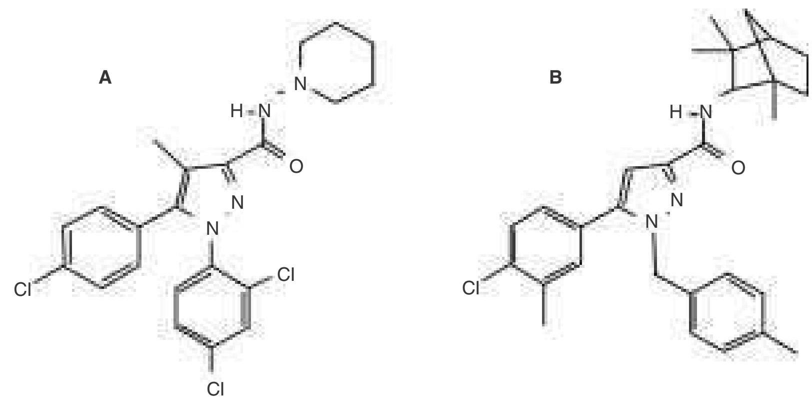
Several anandamide congeners have been synthesized (Abadji et al. 1994), among them (*R*)-(+)-α-methanandamide that possesses both a four-fold higher affinity for the CB_1 receptor and a greater catabolic resistance than anandamide. Fatty acid-based compounds have been synthesized that mimic the structure of anandamide, but act as inhibitors of the catabolic amidase enzyme, the "fatty acid amide hydrolase" (FAAH) (Di Marzo 1998).

AM-404 is a synthetic fatty amide that acts as a selective inhibitor of anandamide transport, thus preventing cellular re-uptake of anandamide (Beltramo et al. 1997) and increasing circulating anandamide levels (Giuffrida et al. 2001).

Therapeutic Potential of Antagonists

SR141716A (Figure 11) has been shown to improve memory in rodents (Terranova et al. 1996) and cause hyperalgesia (Jaggar et al. 1998). This

FIGURE 11. Cannabinoid receptor antagonists, SR 141716A (A), a selective CB_1 receptor antagonist, and SR 144528 (B), a selective CB_2 receptor antagonist.



antagonist was also able to block the psychological and physiological effects of THC in humans in a dose-dependent manner (Huestis 2001). A possible therapeutic potential was proposed for obesity (Huestis et al. 2001), schizophrenia (Huestis et al. 2001), in conditions with lowered blood pressure, e.g., liver cirrhosis (Wagner et al. 2001), Parkinson's disease (Di Marzo et al. 2000b), Huntington's disease (Müller-Vahl et al. 1999), alcohol dependency (Vacca et al. 2002, Racz et al. 2003) and to improve memory in Alzheimer's disease (Huestis et al. 2001).

TOLERANCE AND DEPENDENCY

Tolerance

Tolerance develops to most of the THC effects (Romero et al. 1997), among them the cardiovascular, psychological and skin hypothermic effects (Jones et al. 1976, Stefanis 1978), analgesia (Bass and Martin 2000), immunosuppression (Luthra et al. 1980), corticosteroid release (Miczek and Dixit 1980), and disruption of the hypothalamo-hypophyseal axis (Smith et al. 1983), causing alterations in endocannabinoid formation and contents in the brain (Di Marzo et al. 2000). In a 30-day study, volunteers received daily doses of 210 mg oral THC and developed tolerance to cognitive and psychomotor impairment and to the

psychological high by the end of the study (Jones and Benowitz 1979). After a few days an increased heart rate was replaced by a normal or a slowed heart rate. Tolerance develops also to orthostatic hypotension (Benowitz and Jones 1975).

Tolerance can mainly be attributed to pharmacodynamic changes, presumably based on receptor downregulation and/or receptor desensitisation (Di Marzo et al. 2000, Rubino et al. 2000b). Rate and duration of tolerance varies with different effects. Rats receiving THC over a period of five days exhibited a decreased specific binding ranging from 20 to 60% in different receptor sites of the brain compared to controls (Romero et al. 1997). However, in another study no significant alteration in receptor binding was observed after chronic administration of THC resulting in a twenty-sevenfold behavioral tolerance (Abood et al. 1993). Chronic administration of anandamide as well resulted in behavioral tolerance without receptor downregulation (Rubino et al. 2000a), and it was proposed that desensitization of the CB_1 receptor might account for this observation (Rubino et al. 2000a). Tolerance has been observed to occur together with modified biotransformation activities with regard to mitochondrial oxygen consumption, monooxygenase activities, and the content of liver microsomal cytochrome P450 (Costa et al. 1996). However, only a small proportion of tolerance can be attributed to changes in metabolism (Hunt and Jones 1980).

Withdrawal and Dependency

After abrupt cessation of chronic dosing with high doses of THC, withdrawal has been observed in humans (Georgotas and Zeidenberg 1979, Jones and Benowitz 1976). Subjects complained of inner unrest, irritability, and insomnia and presented "hot flashes," sweating, rhinorrhea, loose stools, hiccups, and anorexia. Withdrawal symptoms in humans are usually mild and the risk for physical and psychic dependency is low compared to opiates, tobacco, alcohol, and benzodiazepines (Anthony et al. 1994, Kleiber et al. 1997, Roques 1998). A review of several indicators of the abuse potential of oral dronabinol in a therapeutic context found little evidence of such a problem (Calhoun et al. 1998).

THERAPEUTIC USES

Cannabis preparations have been employed in the treatment of numerous diseases, with marked differences in the available supporting

data (British Medical Association 1997, Grotenhermen and Russo 2002, House of Lords 1998, Joy et al. 1999). Besides phytocannabinoids, several synthetic cannabinoid derivatives are under clinical investigation that are devoid of psychotropic effects, and modulators of the endocannabinoid system (re-uptake inhibitors, antagonists at the CB receptor, etc.) will presumably follow.

Clinical studies with single cannabinoids or, less often with whole plant preparations (smoked marijuana, encapsulated cannabis extract), have often been inspired by positive anecdotal experiences of patients employing crude cannabis products (usually without legal sanction). The anti-emetic (Dansak 1997), and the appetite enhancing effects (Plasse et al. 1991), muscle relaxation (Clifford 1983), analgesia (Noyes and Baram 1974), and therapeutic use in Tourette's syndrome (Müller-Vahl et al. 1997) were all discovered or re-discovered in this manner.

Incidental observations have also revealed therapeutically useful effects. This occurred in a study of Volicer et al. (1997) in patients with Alzheimer's disease wherein the primary issue was an examination of the appetite-stimulating effects of Δ^9-THC. Not only appetite and body weight increased, but disturbed behavior among the patients also decreased following the intake of the drug. The discovery of decreased intraocular pressure with THC administration in the beginning of the 1970s was also serendipitous (Hepler and Frank 1971), when several research groups screened for effects of marijuana on the human body.

HIERARCHY OF THERAPEUTIC EFFECTS

Possible indications for cannabis preparations have been extensively reviewed (British Medical Association 1997, Grinspoon and Bakalar 1993, Grotenhermen and Russo 2002, Grotenhermen 2002a, House of Lords 1998, Joy et al. 1999, Mathre 1997, Mechoulam 1986). To do justice to the scientific evidence with regard to different indications, a hierarchy of therapeutic effects can be devised, with established, relatively well-confirmed, less confirmed and effects at a basic research stage. However, the history of research into the therapeutic benefits of cannabis and cannabinoids has demonstrated that the scientific evidence for a specific indication does not necessarily reflect the actual therapeutic potential for a given disease, but sometimes obstacles to clinical research.

Established Effects

Marinol™ (dronabinol, Δ^9-THC) is approved for medical use in refractory nausea and vomiting caused by antineoplastic drugs used for the treatment of cancer (Abrahamov et al. 1995, Dansak 1997, Lane et al. 1991, Sallan et al. 1980) and for appetite loss in anorexia and cachexia of HIV/AIDS patients (Beal et al. 1995, Beal et al. 1997, Plasse et al. 1991). These effects can be regarded as established effects for THC and cannabis. THC is also effective in cancer cachexia (Jatoi et al. 2002) and nausea induced by syrup of ipecac (Soderpalm et al. 2001). Cesamet™ (nabilone) is approved for nausea and vomiting associated with cancer chemotherapy.

Relatively Well-Confirmed Effects

Spasticity due to spinal cord injury (Brenneisen et al. 1996, Maurer et al. 1990, Petro 1980), multiple sclerosis (Brenneisen et al. 1996, Killestein et al. 2002, Martyn et al. 1995, Meinck et al. 1989, Petro 1980, Petro and Ellenberger 1981, Ungerleider et al. 1987), and other reasons (Lorenz 2002), chronic painful conditions, especially neurogenic pain (Elsner et al. 2001, Holdcroft et al. 1997, Maurer et al. 1990, Notcutt et al. 2001a, Notcutt et al. 2001b, Noyes et al. 1975a, Noyes et al. 1975b, Petro 1980, Wade et al. 2003), movement disorders (including Tourette's syndrome, dystonia and levodopa-induced dyskinesia) (Clifford 1983, Fox et al. 2002, Hemming and Yellowlees 1993, Müller-Vahl et al. 1999, Müller-Vahl et al. 2002, Müller-Vahl et al. 2003, Sandyk and Awerbuch 1998, Sieradzan et al. 2001), asthma (Hartley et al. 1978, Tashkin et al. 1974, Williams et al. 1976) and glaucoma (Crawford and Merritt 1979, Hepler and Frank 1971, Hepler and Petrus 1976, Merritt et al. 1980, Merritt et al. 1981) can be regarded as relatively well-confirmed effects with small placebo controlled trials demonstrating benefits. However, results were sometimes conflicting. In contrast to other studies, Clermont-Gnamien et al. (2002) did not find any therapeutic effect of oral dronabinol titrated to the maximum dose of 25 mg/day (mean dose: 15 ± 6 mg), during an average of 55 days in seven patients with chronic refractory neuropathic pain. Killestein et al. (2002) were unable to find any benefits of THC and capsulated cannabis extract in MS patients with severe spasticity but doses applied (2×2.5 mg or 2×5 mg THC) were probably too low to get the desired therapeutic effects.

Less Confirmed Effects

There are several indications in which mainly case reports suggest benefits. These are allergies (Schnelle et al. 1999), inflammation (Joy et al. 1999), epilepsy (Gordon and Devinsky 2001), intractable hiccups (Gilson and Busalacchi 1998), depression (Beal et al. 1995), bipolar disorders (Grinspoon and Bakalar 1998), anxiety disorders (Joy et al. 1999), dependency to opiates and alcohol (Mikuriya 1970, Schnelle et al. 1999), withdrawal symptoms (Mikuriya 1970), and disturbed behavior in Alzheimer's disease (Volicer et al. 1997).

BASIC RESEARCH STAGE

Basic research shows promising possible future therapeutic uses, among them neuroprotection in hypoxia and ischemia due to traumatic head injury, nerve gas damage and stroke (Hampson 2002, Mechoulam and Shohami 2002). Some immunological mechanisms of THC hint to possible benefits in autoimmune diseases, such as multiple sclerosis, arthritis, and Crohn's disease (Melamede 2002). In a murine model of multiple sclerosis, cannabinoids significantly improved the neurological deficits in a long-lasting way. On a histological level they reduced microglial activation and decreased the number of CD4+ infiltrating T cells in the spinal cord (Arevalo-Martin et al. 2003). Another group found that amelioration of clinical disease in the same MS model was associated with downregulation of myelin epitope-specific Th1 effector functions (delayed-type hypersensitivity and IFN-gamma production) and the inhibition of the proinflammatory cytokines, TNF-alpha, interleukin 1-beta, and interleukin-6 (Croxford and Miller 2003). Several phytocannabinoids possess an anti-allergic potential. THC and cannabinol attenuated the increase of the interleukins IL-2, IL-4, IL-5, and IL-13 in reaction to sensitization with ovalbumin in mice. In addition, the elevation of serum IgE and the mucus overproduction induced by ovalbumin was markedly attenuated by the two cannabinoids (Jan et al. 2003).

Anti-neoplastic activity of THC came into the focus of research after a long-term animal study, designed to investigate THC's potential carcinogenicity, resulted in better survival of rats dosed with THC than controls due to lower incidence for several types of cancer (Chan et al. 1996). Frequency of testicular interstitial cell, pancreas and pituitary gland adenomas in male rats, mammary gland fibroadenoma and uterus stromal polyp in female rats was reduced in a dose-related manner.

Later studies showed that cannabinoids exerted antineoplastic activity in malignant gliomas (Jacobsson et al. 2001, Sanchez et al. 2001) and malignant skin tumors (Casanova et al. 2003). CB1 and CB2 receptor agonists were both effective. Cannabinoids seem to be able to control the cell survival/death decision (Guzman et al. 2001). Thus, cannabinoids may induce proliferation, growth arrest, or apoptosis in a number of cells depending on dose (Guzman et al. 2001). Cannabinoids were also shown to inhibit angiogenesis of malignant gliomas by at least two mechanisms, direct inhibition of vascular endothelial cell migration and survival as well as the decrease of the expression of proangiogenic factors (Blazquez et al. 2003). A first human Phase I-II trial to investigate the tolerability and efficacy of intracranially applied THC (dronabinol) in glioblastoma multiforme is under way in Spain.

Other fields of research are disorders of circulation and blood pressure (Ralevic and Kendall 2001, Wagner et al. 2001). In rats, daily application of a CB_1 agonist after experimental infarction prevented signs of heart failure, endothelial dysfunction and hypotension; however, the cannabinoid also increased left-ventricular end-diastolic pressure, which may be negative in the long run (Wagner et al. 2003).

Several effects observed in animal studies provide the basis for further research, among them effects against diarrhea in mice (Izzo et al. 2000), inhibition of bronchospasm provoked by chemical irritants in rats (Calignano et al. 2000), and stabilization of respiration in sleep-related breathing disorders (e.g., apnea) (Carley et al. 2002).

Some effects that are usually regarded as side effects may be also of advantage in certain pathological situations, among them the disturbance of short-term memory. Patients suffering from posttraumatic stress disorders want to forget and there are anecdotal reports on their benefits from cannabis (Gieringer 2002). Animal research has demonstrated that CB_1-deficient mice showed strongly impaired short-term and long-term extinction of aversive memories (Marsicano et al. 2002), which may explain some of the anxiety reducing effects in posttraumatic stress disorder and similar conditions (Sah 2002).

DRUG INTERACTIONS

Interactions with other drugs may depend on activity on similar effector systems or metabolic interactions (Pryor et al. 1976). Since cannabinoids are strongly bound to proteins, interactions with other protein bound drugs may also occur. They might also interact with

drugs that, such as THC, are metabolized by enzymes of the cytochrome P-450 complex. However, there was only a minor influence of cannabis smoking and oral dronabinol on pharmacokinetic parameters of antiretroviral medication used in HIV infection and metabolized by cytochrome P-450 enzymes, and the use of cannabinoids was regarded as unlikely to impair antiretroviral efficacy (Kosel et al. 2002). Tobacco and cannabis smoking cessation was reported to result in elevated blood levels of antipsychotic medication (clozapine or olanzapine), due to cessation of induction of cytochrome $P450_{1A2}$ (CYP1A2) by smoke constituents (Zullino et al. 2002).

Other medicines may enhance or attenuate certain actions of THC or certain actions of these medicines may be enhanced or attenuated by THC (Hollister 1999, Sutin and Nahas 1999). Moreover, it is possible that certain effects are enhanced and others reduced, as is the case with phenothiazines applied against side effects of cancer chemotherapy. In a study by Lane et al. (1991), a combination of prochlorperazine and dronabinol was more effective in reducing unwanted effects of the antineoplastic medication than the phenothiazine alone and the incidence of cannabinoid-induced adverse effects was decreased when dronabinol was combined with prochlorperazine, which also has antipsychotic properties. Cannabis, caffeine and tobacco reduced the blood pressure reactivity protection of ascorbic acid, probably through their dopaminergic effects (Brody and Preut 2002).

Of greatest clinical relevance is reinforcement of the sedating effects of other psychotropic substances (alcohol, benzodiazepines), and the interaction with substances that act on heart and circulation (amphetamines, adrenaline, atropine, beta-blockers, diuretics, tricyclic antidepressants, etc.) (Hollister 1999, Sutin and Nahas 1999).

A number of additive effects may be desirable, such as the enhancement of muscle relaxants, bronchodilators and anti-glaucoma medication (Pate 2002), of analgesia by opiates (Welch and Eads 1999, Cichewicz and McCarthy 2003), the antiemetic effect of phenothiazines (Lane et al. 1991), and the antiepileptic action of benzodiazepines (Koe et al. 1985). THC may antagonize the antipsychotic actions of neuroleptics (Sutin and Nahas 1999) and may improve their clinical responsiveness in motor disorders (Moss et al. 1989). A combination with other drugs may be desirable not only to reduce side effects of the single drugs but also to prevent the development of tolerance. In animal studies, tolerance to morphine was reduced by simultaneous administration of THC (Cichewicz and Welch 2003). Chronic treatment with high doses of oral morphine produced a threefold tolerance of pain-reducing effects. Tol-

erance to morphine was prevented in groups receiving a daily co-treatment with low doses of THC (Cichewicz and Welch 2003).

Since the endocannabinoid system is linked with hormonal control there may be interactions in this area. The progesterone receptor inhibitor mifepristone, which is approved for the termination of early pregnancy, and the glucocorticoid synthesis inhibitor metyrapone was recently shown to potentiate the sedating effects of high THC doses in mice (Pryce et al. 2003).

The cyclooxygenase inhibitors indomethacin, acetylsalicylic acid, and other non-steroidal anti-inflammatory drugs antagonize THC effects. Indomethacin significantly reduced subjective "high" (Perez-Reyes et al. 1991), tachycardia (Perez-Reyes et al. 1991), decrease of contractile performance in heart muscle (Bonz et al. 2003) and decrease of intraocular pressure following topical THC (eye drops) (Green et al. 2001), reflecting the involvement of cyclooxygenase activity in several THC effects.

CONCLUSIONS

The discovery, within the past 15 years, of a system of specific cannabinoid receptors in humans and their endogenous ligands has strongly stimulated research with about 800 articles published in Medline listed journals in 2002, compared to about 250 twenty years ago. It becomes apparent that the endocannabinoid system is playing a major role in signal transduction in neuronal cells, and arachidonylethanolamide (anandamide) seems to be a central inhibitory compound in the central nervous system (Mechoulam et al. 1998).

Mechanisms of action of cannabinoids are complex, not only involving activation of and interaction at the cannabinoid receptor, but also activation of vanilloid receptors (Jacobsson et al. 2001), influence of endocannabinoid concentration (Bisogno et al. 2001), antioxidant activity (Hampson 2002), metabolic interaction with other compounds, and several others. There is still much to learn about the physiological role of the natural ligands to the CB receptors and about long-term effects of cannabis use. However, due to the millennia-long use of cannabis for recreational, religious and medicinal purposes, which in recent decades was accompanied by scientific investigation in several disciplines, we do not expect to encounter with the medicinal use of cannabinoids the same unpleasant surprises that occasionally occur with newly designed synthetic drugs.

Many people who suffer from severe illnesses have discovered cannabis as a beneficial remedy, and public opinion surveys in Europe and North America show that increasing numbers of citizens reject criminal prosecution of patients who benefit from the drug. The psychotropic and circulatory effects of CB_1 receptor agonists and the stigma of cannabis as a recreational and addicting drug are still major obstacles to the legal therapeutic utilization of the whole range of potentially beneficial effects. Properly designed and executed clinical studies are necessary to verify anecdotal experiences and the results from smaller uncontrolled studies, and to overcome uncertainties and skepticism.

Aside from phytocannabinoids and cannabis preparations, cannabinoid analogues that do not bind to the CB_1 receptor are attractive compounds for clinical research, among them dexanabinol and CT-3. Additional ideas for the separation of the desired therapeutic effects from the psychotropic action comprise the concurrent administration of THC and CBD, the design of CB_1 receptor agonists that do not cross the blood brain barrier, and the development of compounds that influence endocannabinoid levels by inhibition of their membrane transport (transport inhibitors) or hydrolysis (FAAH inhibitors). For example, blockers of anandamide hydrolysis were able to reduce anxiety in animal tests (Kathuria et al. 2003). These benzodiazepine-like properties were accompanied by augmented brain levels of anandamide and were prevented by CB_1 receptor blockade. It is remarkable that FAAH inhibitors may already be in clinical use as proposed by Fowler (2003). The non-steroidal anti-inflammatory agent fluriprofen inhibits the metabolism of FAAH and intrathecally administrated fluriprofen reduced inflammatory pain by a mechanism that was blocked by a CB_1 receptor antagonist (Fowler 2003).

The future will show which drugs that target the endogenous cannabinoid system will follow dronabinol and nabilone into the pharmacy and which indications will prove successful in clinical trials.

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Cannabis as a Substitute for Alcohol: A Harm-Reduction Approach

Tod H. Mikuriya

ABSTRACT. Ninety-two Northern Californians who use cannabis as an alternative to alcohol obtained letters of approval from the author. Their records were reviewed to determine characteristics of the cohort and efficacy of the treatment, which was defined as reduced harm to the patient. All patients reported benefit, indicating that for at least a subset of alcoholics, cannabis use is associated with reduced drinking. The cost of alcoholism to individual patients and society at large warrants testing of the cannabis-substitution approach and study of the drug-of-choice phenomenon.

KEYWORDS. Addiction, alcohol, alcoholism, cannabis, depression, drug-of-choice, harm reduction, marijuana, pain

INTRODUCTION

Physicians who treat alcoholics are familiar with the cycle from drunkenness and disinhibition to withdrawal, drying out, and apology for behavioral lapses, accompanied over time by illness and debility as

Tod H. Mikuriya, MD, is Psychiatric Medical Consultant, Berkeley, CA, and President, California Cannabis Research Medical Group.

Address correspondence to: Tod H. Mikuriya, MD, 1186 Sterling Avenue, Berkeley, CA 94798-1757 (E-mail: drtod@mikuriya.com).

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the patient careens from one crisis to another. "Harm reduction" is a treatment approach that seeks to minimize the occurrence of drug/alcohol addiction and its impacts on the addict/alcoholic and society at large. A harm-reduction approach to alcoholism adopted by 92 of my patients in Northern California utilizes the substitution of cannabis, with its relatively benign side-effect profile, as the intoxicant of choice.

No clinical trials of the efficacy of cannabis as a substitute for alcohol are reported in the literature, and there are no papers directly on point prior to my own account (Mikuriya 1970) of a patient who used cannabis consciously and successfully to discontinue her problematic drinking.

There are ample references, however, to the use of cannabis as a substitute for opiates (Birch 1889) and as a treatment for delirium tremens (Clendinning 1843; Moreau 1845), which were among the first uses by European physicians. The 1873 Indian Government Finance Department Resolution recommended against suppressing cannabis use for fear that people (p. 1395) "would in all probability have recourse to some other stimulant such as alcohol."

The Indian Hemp Drugs Commission Report of (1893-1894) articulated the same concern (p. 359): ". . . driving the consumers to have recourse to other stimulants or narcotics which may be more deleterious." Birch (1889) described a patient weaned off alcohol by use of opiates who then became addicted and was weaned off opiates by use of cannabis. He noted (p. 625), "Ability to take food returned. He began to sleep well; his pulse exhibited some volume; and after three weeks he was able to take a turn on the verandah with the aid of a stick. After six weeks he spoke of returning to his post, and I never saw him again."

Birch feared that cannabis itself might be addictive, and recommended against revealing to patients the effective ingredient in their elixir (p. 625), "Upon one point I would insist–the necessity of concealing the name of the remedial drug from the patient, lest in his endeavor to escape from one form of vice he should fall into another, which can be indulged with facility in any Indian bazaar." This stern warning may have undercut interest in the apparently successful two-stage treatment he was describing.

At the turn of the 19th century in the United States, cannabis was listed as a treatment for delirium tremens in standard medical texts (Edes 1887; Potter 1895) and manuals (Lilly 1898; Merck 1899; Parke Davis 1909). Since delirium tremens is associated with advanced alcoholism, we can adduce that patients who were prescribed cannabis and used it on a long term basis were making a successful substitution.

By 1941, due to its prohibition, cannabis was no longer a treatment option, but attempts to identify and synthesize its active ingredients continued (Loewe 1950). A synthetic THC called pyrahexyl was made available to clinical researchers, and one paper from the postwar period reports its successful use in easing the withdrawal symptoms of 59 out of 70 alcoholics (Thompson and Proctor 1953).

In 1970 the author reported (Mikuriya 1970) on Mrs. A., a 49-year-old female patient whose drinking had become problematic. The patient had observed that when she smoked marijuana socially on weekends she decreased her alcoholic intake. She was instructed to substitute cannabis any time she felt the urge to drink. This regimen helped her to reduce her alcohol intake to zero. The paper concluded (p. 175), "It would appear that for selected alcoholics the substitution of smoked cannabis for alcohol may be of marked rehabilitative value. Certainly cannabis is not a panacea, but it warrants further clinical trial in selected cases of alcoholism."

The warranted research could not be carried out under conditions of prohibition in the USA, but in private practice and communications with colleagues I encountered more patients like Mrs. A. and generalized that somewhere in the experience of certain alcoholics, cannabis use is discovered to overcome pain and depression, target conditions for which alcohol is originally used, but without the disinhibited emotions or the physiologic damage. By substituting cannabis for alcohol, patients were able to reduce the harm their intoxication caused themselves and others.

Although the increasing use of marijuana starting in the late '60s had renewed interest in its medical properties, including possible use as an alternative to alcohol (Scher 1971), meaningful research was prevented until the 1990s, when the establishment of "buyers clubs" in California created a potential database of patients who were using cannabis to treat a wide range of conditions. The medical marijuana initiative passed by voters in 1996 mandated that prospective patients obtain a doctor's approval in order to treat a given condition with cannabis, resulting in an estimated 30,000 physician approvals as of May 2002 (Gieringer 2003).

In a review of my records in the spring of 2002, 92 patients were identified as using cannabis to treat alcohol abuse and related problems. This paper describes characteristics of that cohort and the results of their efforts to substitute cannabis for alcohol.

METHODOLOGY

Identifying Alcoholism

The initial consultation (20 minutes) provided multiple opportunities to identify alcoholism as a problem for which treatment with cannabis might be appropriate. The intake form asked patients to state their reason for contacting the doctor, and enabled them to prioritize their present illnesses and describe the course of treatment to date. The form also asked patients to identify any non-prescribed psychoactive drugs they were taking (including alcohol), and invited remarks. A specific question concerned injuries incurred "while or after consuming alcohol." Examination of medical records provided an additional opportunity to identify alcohol abuse, as did the taking of a verbal history.

Evaluating Efficacy

At follow-up visits (typically at 12-month intervals), patients were asked to list the conditions they had been treating with cannabis and to evaluate their status as "stable," "improved," or "worse." Patients were asked to evaluate the efficacy of cannabis (five choices from "very effective to "ineffectual") and to describe any adverse events. Patients were also asked to describe any changes in their "living and employment situation," and if so, to elaborate. The question about use of non-prescribed psychoactive drugs, including alcohol, was repeated. Comparison of responses in a given patient's initial and follow-up questionnaires enabled assessment of the utility of cannabis as an alternative to alcohol.

Patient Background

Gieringer (2003) notes that (p. 55), "Many patients who find marijuana helpful for otherwise intractable complaints report that their physicians are fearful of recommending it, either because of ignorance about medical cannabis, or because they fear federal punishment or other sanctions. This is especially true in regions where the use of marijuana is less familiar and accepted." The patients whose records form the basis for this study were all seen in ad hoc settings arranged by local cannabis clubs, 88 in rural counties of Northern California, four in the San Francisco Bay Area. They form a special but not unique subset, having intentionally sought out a physician whose clinical use of canna-

bis and confidence in its versatility and relative safety was extensive and well known in their communities.

A majority of the patients identified themselves as blue-collar workers: carpenter (5), construction (3), laborer (3), waitress (3), truck driver (3), fisherman (3), heavy equipment operator (3), painter (2), contractor (2), cook (2), welder (2), logger (2), timber faller, seaman, hardwood floor installer, bartender, building supplies, house caretaker, ranch hand, concrete pump operator, cable installer, silversmith, stone mason, boatwright, auto detailer, tree service-handyman-cashier, nurseryman, glazier, gold miner, carpet layer, carpenter's apprentice, landscaper, river guide, screenprinter, and glassblower.

Eleven were unemployed or did not list an occupation; four were disabled, two retired, and two patients defined themselves as mothers. Others were in sales (5), musicians (5), clerical workers (3), paralegal, teacher, actor, actress, artist, sound engineer, and computer technician. Eighty-two of the patients were male. Patients' ages ranged from 20 to 69. Twenty-nine were in their twenties; 16 in their thirties; 24 in their forties; 20 in their fifties; and three in their sixties. Exactly half (46 patients) had taken some college courses, but only four had college degrees. Five did not complete high school. Thirteen were veterans, all branches of the Armed Forces being represented. All but six (five native-Americans, one African-American) were Caucasian. Slightly more than half (49) reported being raised by at least one addict/alcoholic parent.

Prioritizing Alcoholism

Fifty-nine of the patients identified alcoholism or cirrhosis of the liver as their primary medical problem. Secondary and tertiary problems reported by this group were depression (19), pain (17), insomnia (15), arthritis (8), anxiety/stress (8), PTSD (3), cramps (4), hepatitis C (4), gastritis (2), ADHD (2), cramps/PMS (3), scoliosis, irritable bowel syndrome, glaucoma, and anorexia.

Thirty-three patients identified themselves as alcohol abusers, but reported other problems as more significant: pain (12), depression (7), anxiety/stress (6), headache/migraines (5), insomnia (5), head injuries (3), bipolar disorder (3), arthritis (2), asthma (2), spinal cord injury/disease (2), gastritis (2), paraplegia, ADHD, multiple broken bones, Parkinson's, and cramps.

Nineteen patients reported having been injured while or after drinking heavily.

Fourteen had incurred legal problems or been ordered into rehab programs.

Cannabis Use/Awareness of Medicinal Effect

Patients were asked when they started using cannabis and when they realized it exerted a medicinal effect. Three reported first using at age 9 or younger; 61 between ages 10 and 19; nine began using in their 20s; three in their 30s; six in their 40s; two at age 50; and one at age 65. Twenty-four patients reported realizing immediately upon using cannabis that it exerted a beneficial medical effect. Some of their responses still seem to reflect their relief at the time:

- "In 1980 I had quit drinking for a month. My niece asked me if I ever tried marijuana to calm me down. So I tried it and it worked like a miracle."
- "Helped pain very much! Helped sleep–excellent."

Thirty-five patients answered ambiguously with respect to time: "When realized preferred to alcohol," for example, or, "when I smoked when suffering."

Seven reported becoming aware of medical effect within a year of using cannabis. Ten became aware within one to five years. Three became aware of medical effect 12-15 years after first using. Ten became aware between 20 and 30 years after first using. All but one of these patients had resumed using cannabis after years of abstinence.

Use of OTC and Prescription Drugs

Patients were asked to list other drugs (prescribed, over-the-counter, and herbal) that they were currently using or had used in the past to treat their illnesses. Most common of the prescription drugs were SSRIs (31), opiates (23), NSAIDs (18), disulfuram (15), and Ritalin® (methylphenidate) (8).

Delivery Systems

Seventy-eight patients smoked joints, the average amount being one joint a day (assuming 3.5 joints per 1/8 ounce of high-quality mari-

juana). Twelve patients reported using a pipe, and three owned vaporizers. All were strongly advised that smoking involves an assault on the lungs, and that vaporization is a safer method of inhaling cannabinoids.

OBSERVATIONS

Alcoholic Parents

A slight majority of patients (51) reported being raised by at least one alcoholic parent. This is not surprising. The children of alcoholics enter adulthood with two strikes. They have endured direct emotional abuse and/or abandonment by parent(s), and they lack role models for coping with uncomfortable feelings other than by inebriation. It is to be expected that many, when encountering problems early in life, are treated with, or seek out, mind-altering drugs.

Reported Efficacy

As could be expected among patients seeking physician approval to treat alcoholism with cannabis, all reported that they'd found it "very effective" (45) or "effective" (38). Efficacy was inferred from other responses on seven questionnaires. Two patients did not make follow-up visits but had reported efficacy at the initial interview.

Nine patients reported that they had practiced total abstinence from alcohol for more than a year and attributed their success to cannabis. Their years in sobriety: 19, 18, 16, 10, 7, 6, 4 (2), and 2.

Patients who reported a return of symptoms when cannabis was discontinued (19), ranged from succinct to dramatic:

- "I started drinking a lot more."
- "More anxiety, less happiness."
- "Use alcohol when cannabis isn't available."
- "If I don't have anything to smoke, I usually drink a lot more."
- "I quit using cannabis while I was in the army and my drinking doubled. I was also involved in several violent incidents due to alcohol.
- "My caretaker got arrested and I lived too far from the city to purchase at a club, and I started doing heroin again and almost killed myself and some of my friends."

- "Stress level becomes higher, become more uptight. Went back to drinking in the 1970s."–A female patient with 19 years of sobriety.

Several patients specifically noted that cannabis use reduced the craving for alcohol:

- "I crave alcohol when I can't smoke marijuana."
- "Had to quit drinking at 48 yrs. old. Found cannabis helped stop the urge to drink."–A 69-year-old commercial fisherman.

Three patients reported a sad irony: they had "fallen off the wagon" when they had to stop using cannabis in anticipation of drug tests. Patient S., a 27-year-old cable installer, had six alcohol-related arrests by age 21, ". . . after not smoking herb (for probation drug test) and blacking out on alcohol, I found my drinking getting out of hand and I began getting into more trouble." He later relapsed when denied use of cannabis at a residential treatment facility.

Cannabis for Analgesia

The large number of patients using cannabis for pain relief (29) reflects the high percentage of blue-collar workers who suffer musculoskeletal injury during their careers. As expressed by a carpenter, "Nobody gets to age 40 in my business without a bad back." Nurses who must lift gurneys, farm workers, desk-bound clerical workers, and many others are also prone to chronic back and neck pain.

Fights and accidents (vehicular, sports- and job-related) also create chronic pain patients, many of whom self-medicate with alcohol.

Eighteen patients reported having been injured while or after drinking heavily. This comment by a 26-year-old truck driver describes a typical chain-reaction of alcohol-induced trouble: "Injured in a fight after consuming alcohol, resulted in staph infection of right knuckle, minor surgery and four days in hospital." Injuries suffered while drunk add to pain and the need for relief by alcohol, or a less destructive alternative.

A total of 29 patients reported using cannabis for both pain relief and as an alternative to alcohol. A 47-year-old landscaper was run over by a vehicle at age 5, requiring multiple surgeries and leaving him with pins in his right ankle: "Given pain pills for my right ankle, I got too drowsy. Smoked herb to relieve pain." After he had to discontinue cannabis use,

he reported, "was unable to ease pain in ankle without herb, and drink when unable to have cannabis to smoke."

Cannabis for Mood Disorders

Twenty-six patients reported using cannabis to treat depression (44 if the category is expanded to include anxiety, stress, and PTSD), and their comments frequently touched on the negative synergies between mood disorders and alcoholism. A 44-year-old paralegal, suffering from depression, alcoholism, and PMS, noted simply, "Alcohol causes more depression." When she did not have access to cannabis, she noted, "Alcohol consumption increases and so does depression." At her initial visit she reported consuming 5-10 drinks/day. At a follow-up visit (after 16 months) she had confined her consumption to weekend usage.

A 33-year-old river guide (and decorated Army vet) put it this way: "I have had a problem with violence and alcohol for a long time and I have a rap sheet to prove it. None of the problems occurred while using cannabis. Not only does cannabis prevent my violent tendencies, but it also helps keep me from drinking." On his follow-up visit (12 months) this patient reported improved communication with family members and fewer problems relating to other people. His alcohol consumption had decreased from 36 drinks/week to zero (one month of sobriety).

Patient L.G. presented initially at age 35 as homeless and unemployed, suffering "severe depression. Anxiety. Pain." Her problem with alcohol was inferred from her response concerning non-medical-psychoactive drug use: "I drink and smoke too much–started when I couldn't get marijuana." L.G. had requested a recommendation for cannabis from a Humboldt County physician but, as she recounted, "I'm paranoid and local doctors are scared, too. They gave me Paxil® [paroxetine] and stop smoking pamphlet." At a follow-up visit (14 months), L.G. reported a change in circumstance: "Now have a room. But am on G.R. [General Relief] and am paying too much." She was still using alcohol "a little. I'm doing good dealing with not drinking. Being able to medicate with cannabis has helped a lot." Eighteen months later the pattern hadn't changed: "Alcohol several times/week. Depends on if I have cannabis, stress still triggers."

Fewer Adverse Side-Effects

Compared with NSAIDs, steroids, SSRIs, opioids, and benzodiazepines, cannabis has a benign side-effect profile. In acute conditions

these other drugs may be tolerable, but taking them to treat chronic conditions may be worse than the illness. Patients' comments on their prescribed analgesics and anti-depressants tended to be negative with respect to efficacy (22), side-effects (26) and cost (15), not surprising, perhaps, in a cohort seeking an herbal alternative.

Patient R.B. presented as a 41-year-old alcoholic also suffering from arthritis, pain from knee and ankle surgeries, and depression, for which he had been prescribed Librium® (chlordiazepoxide), Valium® (diazepam), Buspar® (buspirone), Welbutrin® (bupropion), Effexor® (venlafaxine), Zoloft® (sertraline), and Depakote® (valproate) over the years; "No help!" he wrote bluntly. On his return visit (one year) he reported "few relapses" and was able to take some classes.

The dulling effects of Vicodin® (hydrocodone) and other opiates were mentioned by seven patients. As patient P.B. put it, "When I can get Vicodin it helps the pain but I don't like being that dopey."

Patient S.F., whose skull was badly damaged in an accident, also appreciated the pain relief but asserted that opiates (obtained through the Veterans' Administration) "made me paranoid and mean."

Patient C.A., who was diagnosed with attention-deficit hyperactivity disorder (ADHD) in ninth grade, touches on some recurring themes in describing the treatment of his primary illness: "I was prescribed Ritalin and Zoloft. The Ritalin helped me concentrate slightly but caused me to be up all night. The Zoloft made me sick to my stomach and never relieved my stress or depression. I have never been prescribed anything for my insomnia but I usually have to drink some liquor to get to sleep. I think that is a bad thing as I have now begun to drink excessive amounts of whisky, which has really started to affect my stomach."

C.A. first used cannabis at age 19 and became aware of benefits immediately. "I found myself running to the refrigerator and then sleeping better than I had for years." At age 21 he fears permanent damage. "From drinking (I believe) my stomach has been altered, along with my appetite . . . I cannot really eat that much and feel malnourished and weaker than a 21-year-old should. My joints ache constantly and I am not as strong as I used to be. I also fear that I will become or am an alcoholic and I do not want to see myself turn into my dad."

At his follow-up visit (12 months), C.A. reported cannabis to be "very effective." He was employed, "not partying," doing well socially, and trying to give up cigarettes.

Interactions, Positive and/or Negative

Several patients (3) indicated that cannabis had a welcome amplifying effect on the efficacy of other medications. As cannabis comes into wider use in California and elsewhere, it is important that its interactions with other medications be studied and publicized.

DEFINING SUCCESS

The harm-reduction approach to alcoholism is based on the recognition that for some patients, total abstinence has been an unattainable goal. Success is not defined as the achievement of perpetual sobriety. A treatment may be deemed helpful if it enables a patient to reduce the frequency and quantity of alcohol consumption; if drunken episodes and/or blackouts are reduced; and if success in the workplace can be achieved; if specific problems induced by alcohol (suspended driver's license, for example) can be resolved; and if ineffective or toxic drugs can be avoided.

As noted, all of the patients in this study were seeking physician's approval to use cannabis medicinally, a built-in bias that explains the very high level of efficacy reported. However, the vast majority presented with comorbid conditions, and would have qualified for physician's approval to use cannabis whether or not they reported efficacy with respect to alcoholism.

Although medicinal use of cannabis by alcoholics can be dismissed as "just one drug replacing another," lives mediated by cannabis and alcohol tend to run very different courses. Even if use is daily, cannabis replacing alcohol (or other addictive, toxic drugs) reduces harm because of its relatively benign side-effect profile. Cannabis-only usage is not associated with car crashes; it does not damage the liver, the esophagus, the spleen or the digestive tract.

The chronic alcohol-inebriation-withdrawal cycle ceases with successful cannabis substitution. Sleep and appetite are restored, ability to focus and concentrate is enhanced, energy and activity levels are improved, and pain and muscle spasms are relieved. Family and social relationships can be sustained as pursuit of long-term goals ends the cycle of crisis and apology.

Patient M.S., a 42-year-old journeyman carpenter, is a success story from a harm-reduction perspective. At his initial visit he defined his problem as "intermittent explosive disorder," for which he had been prescribed Lithium. Although drinking eight beers a day, he reported

"Cannabis has allowed me to just drink beer when I used to blackout drink vodka and tequila." By the time of a follow-up visit (12 months), Mark had been sober for four months. He also reported, "anger outbreaks less severe, able to complete projects," and, poignantly, "paranoia is now mostly realism." He plans to put his technical skill to use in designing a vaporizer.

THE DOCTOR-PATIENT RELATIONSHIP

As a certified addictionologist, I have supervised both inpatient and outpatient treatment for thousands of patients since 1969. In the traditional alcoholism medical-treatment model, the physician is an authority figure to a patient whose life has spun out of control. The patient enters under coercive circumstances, frequently under court order, with physiologies in toxic disarray. Transference dynamics cast the physician into a parental role, producing the usual parent-child conflicts. After detoxification when cognition has returned from the confusional state of withdrawal, the patient leaves, usually with powers of denial intact. Follow-up outpatient treatment is oriented to Alcoholics Anonymous (AA) and/or pharmacological substitutes.

Treating alcoholism by cannabis substitution creates a different doctor-patient relationship. Patients seek out the physician to confer legitimacy on what they are doing or are about to do. My most important service is to end their criminal status, Aeschalapian protection from the criminal justice system, which often brings an expression of relief. An alliance is created that promotes candor and trust. The physician is permitted to act as a coach or an enabler in a positive sense.

As enumerated by patients, the benefits can be profound: self-respect is enhanced; family and community relationships improve; a sense of social alienation diminishes. A recurrent theme at follow-up visits is the developing sense of freedom as cannabis use replaces the intoxication-withdrawal-recovery cycle, freedom to look into the future and plan instead of being mired in a dysfunctional past and present; and freedom from crisis and distraction, making possible pursuit of long-term goals that include family and community.

RE: ALCOHOLICS ANONYMOUS

Although nine patients made voluntary reference to attending AA meetings (three presently, six in the past), it is likely that many more ac-

tually tried the 12-step program, but the question was not posed on the intake form. A future study should examine the relationship between cannabis-only users and Alcoholics Anonymous. At AA meetings, cannabis use is considered a violation of sobriety. This puts cannabis-only users in a bind. Those who attend meetings can't practice the "rigorous honesty" that AA considers essential to recovery; and those who avoid meetings are denied support and encouragement that might help them to stay sober. Support-group meetings at which cannabis-only users are welcome would be a positive development.

Patient T.H., first seen at age 29, was diagnosed as an alcoholic in 1987 and began attending AA meetings, which he found helpful although he could not achieve sustained sobriety. In 1998, after realizing that cannabis reduced his cravings for alcohol, he received approval to use it. At a follow-up in November '99, he reported, "Have stopped drinking for the first time in many years. I have not taken a drink of alcohol in 14 months. I attribute some credit for this to daily use of cannabis. My life has improved with this treatment."

T.H. was seen again in April 2001 and reported, "I continue to maintain sobriety regarding alcohol. Have not had a drink for 2 1/2 years. I drank alcohol heavy for about 10 years, and had difficulty stopping drinking and staying stopped until I began this treatment. Pain symptoms from back spasms/scoliosis also better."

FACTORS IN DRUG OF CHOICE

Experimentation with drugs and alcohol typically begins in adolescence and participants in the present study fit the well established pattern. It is also in adolescence that most individuals select a drug-of-choice. Factors in the process have not been thoroughly studied, but drug-of-choice is not simply a function of an individual's brain chemistry; social group plays a key role (Carstairs 1951).

Carstairs spent a year in a large village in northern India where the two highest castes, Rajputs and Brahmins, consumed alcohol and cannabis, respectively. The Rajputs were the warriors and governors; they viewed the alcohol-inspired release of emotions, notably sexual and aggressive impulses, as admirable. The Brahmins were the religious leaders whose emphasis on self-denial included (p. 79.), "the avoidance of anger and or any other unseemly expression of personal feelings; abstinence from meat and alcohol is a prime essential."

Carstairs' goal was to understand how the Brahmins could rationalize intoxicant use. He concluded (p. 79):

> There are alternative ways of dealing with sexual and aggressive impulses besides repressing them and then 'blowing them off' in abreactive drinking bouts in which the superego is temporarily dissolved in alcohol. The way which the Brahmins have selected consists in a playing down of all interpersonal relationships in obedience to a common, impersonal set of rules of Right Behavior . . . Whereas the Rajput in his drinking bout knows that he is taking a holiday from his sober concerns, the Brahmin thinks of his intoxication with bhang as a flight not from but toward a more profound contact with reality.

Two aspects of Carstairs' report resonate strongly with my own observations:

1. The disinhibition achieved via alcohol is the Rajput kind, a flight from reality, becoming "blotto," whereas the disinhibition achieved via cannabis is the result of focused or amplified contemplation.
2. "Drug of choice" tends to be–perhaps invariably is–determined by social factors, and, once determined, becomes a defining element of individual self-image, i.e., possible but not easy to change in adulthood. Undoubtedly, alcohol's status as a legal drug that is widely advertised and can be purchased virtually anywhere influences the number of college students and other young adults who make it their initial drug of choice. Perhaps the firmer implementation of California's medical marijuana law will make it possible to study whether young adults with a family history of alcoholism, given no legal obstacle to using cannabis as an alternative to alcohol, would do so, with positive results.

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